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Case Report

Psoriasis and Bullous Pemphigoid: Co-occurence

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Abstract

Psoriasis is a chronic recurrent inflammatory skin disorder. Bullous pemphigoid (BP) is an autoimmune disease characterized by formation of blisters in subepidermal zone. The concurrent occurrence of these two disorders is rare. The pathogenesis behind this occurrence however remains unclear. Here, we are reporting a case of 48-year-old male with psoriasis for 20 years presenting with recent onset BP. Histopathological examination and direct immunofluorescence confirmed the diagnosis of psoriasis and BP.

Key words: Bullous pemphigoid, Histopathology, Immunofluorescence, Methotrexate, Psoriasis

INTRODUCTION

Psoriasis is a T-cell mediated inflammatory disease affecting the skin and joints. Psoriasis has been associated with many other autoimmune diseases such as bullous pemphigoid (BP), linear IgA bullous disorder, epidermolysis bullosa acquisita, lichen planus, rheumatoid arthritis, and atopic dermatitis.[1] Immunobullous disorders occurring with psoriasis is a rare phenomenon, among those, BP is the most common association. BP is a subepidermal autoimmune bullous disorder. Pathogenic mechanisms proposed for occurrence of BP in psoriasis include epitope spreading and Th1 to Th2 response switch.[2]

A 48-year-old male presented with complaints of fluid filled lesions over the inner aspect of bilateral forearm, thighs, and back for the past 1 month. History of itching presents before the onset of lesions. He is a known case of psoriasis for past 20 years on irregular treatment. No history of drug intake before onset of illness. No history of similar complaints in family members.

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Dermatological examination revealed multiple well defined scaly erythematous to hyperpigmented plaques of varying sizes present over the trunk and extremities with positive auspitz sign [Figure 1a]. Multiple tense clear vesicles and bullae of varying sizes present over the inner aspect of forearm, back, and thighs [Figure 1b]. Blisters were present over the normal skin. Few crusted erosions present over the back. Examination of mucosae was normal. Nikolsky sign was negative and bulla spread sign was positive. Biopsy taken from the plaque revealed hyperkeratosis, parakeratosis, acanthosis, and regular elongation of rete ridges [Figure 2a]. Biopsy taken from the intact vesicle revealed sub epidermal split [Figure 2b]. Direct immunofluorescence of perilesional skin showed linear deposits of IgG and C3 at basement membrane zone [Figures 3 and 4].

Based on the clinical findings, histopathological examination and direct immunofluorescence, we arrived at the diagnosis of BP coexisting with chronic plaque psoriasis.

The patient was started on methotrexate 10 mg/week, Doxycycline 100mg o.d., and topical clobetasol propionate for the blisters for 2 weeks. However, the patient continued to develop new blisters, thus methotrexate dose was escalated to 20 mg/week and tablet nicotinamide 250 mg t.d.s. was added. Psoriatic plaques resolved over a period of 6 weeks and there was a significant reduction in bullae after 10 weeks of treatment [Figure 3a and b].

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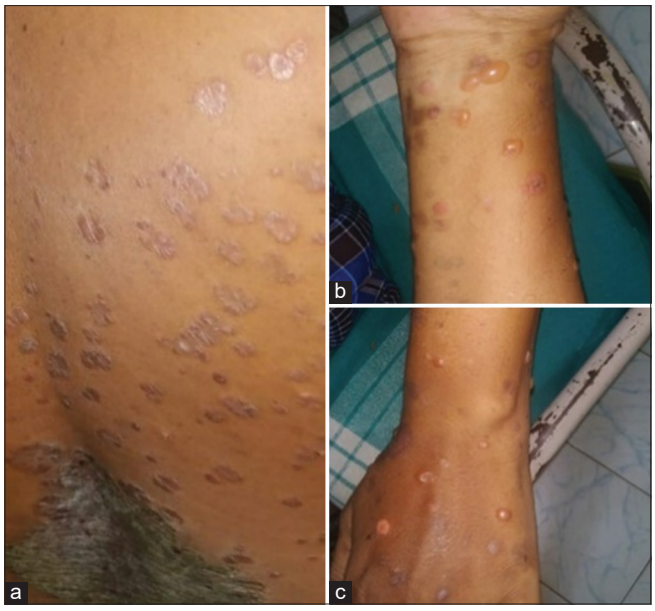

Figure 1: (a) Multiple scaly hyperpigmented plaques over the back, (b) multiple tense vesicles over the flexor aspect of forearm, (c) few vesicles with scaly papules over the dorsum of hands

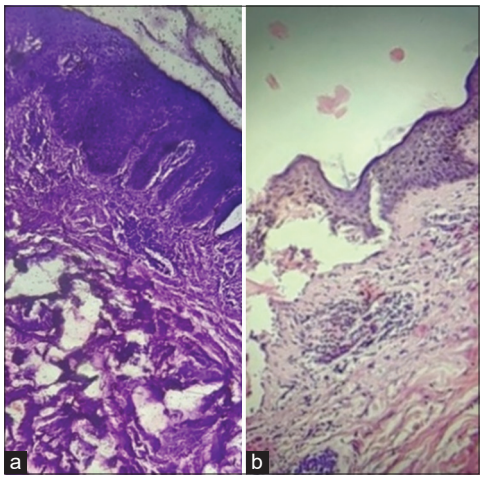

Figure 2: (a) Hyperkeratosis, parakeratosis with regular elongation of rete ridges, (b) biopsy showing sub epidermal split

DISCUSSION

Coexistence of bullous disease and psoriasis was first described by bloom in 1929.[1] Autoimmune bullous diseases occurring with psoriasis include pemphigus vulgaris, pemphigus foliaceous, pemphigus herpetiformis, cicatricial pemphigoid, BP, linear IgA bullous dermatoses, anti-p 200 pemphigoid, and epidermolysis bullosa acquisita. BP is the most common association with psoriasis vulgaris.

BP patients develop autoantibodies predominantly against BPAG1 (BP 230 kDa) and BPAG2 (BP 180 kDa). Several factors such as trauma, drugs, UV light, radiation therapy, and malignancy can trigger BP.

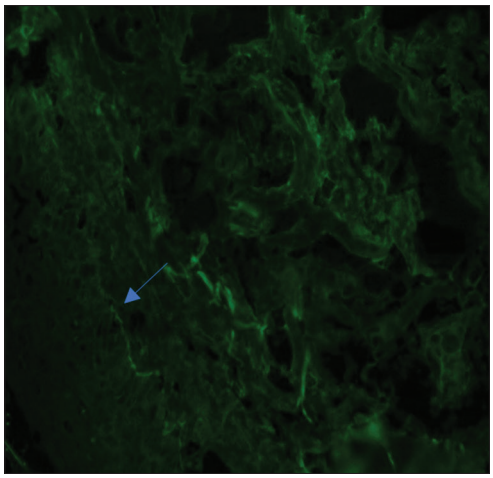

Figure 3: C3 deposits at BMZ

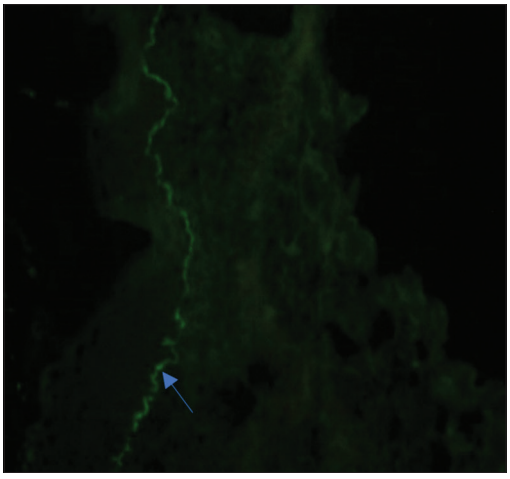

Figure 4: Linear IgG Deposits at BMZ

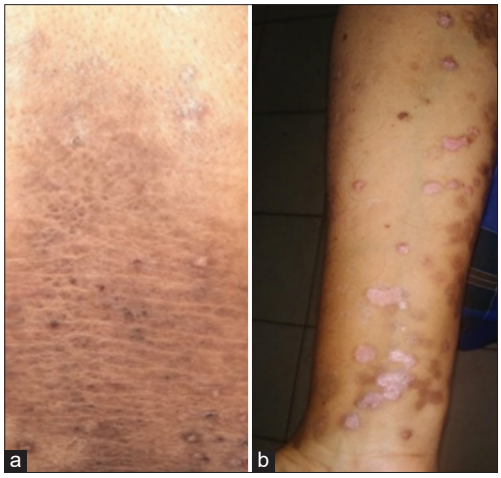

Figure 5: (a) Hyperpigmented patches over the lower back, (b) resolved vesicles with post inflammatory hypopigmentation

Mechanism behind the concomitant occurrence of psoriasis with BP remains unclear. Theories proposed include, concept of epitope spreading, where the inflammatory process in the epidermis triggers the release of previously unexposed antigen resulting in formation of autoantibodies. Dysregulation of T-cell activity in psoriasis results in induction of specific antibodies to basement membrane antigens. Induction of Th 17 causes switching of Th1 to Th2 response leading to production of autoantibodies. Keratinocytes in both psoriasis and BP produce neutrophil chemo attractants, leading to neutrophil infiltration. Neutrophils produce matrix metalloproteinases, which degrade matrix proteins leading to exposure of surface antigens.[2]

Methotrexate is an effective drug for BP associated with psoriasis. Other immunosuppressive drugs such as azathioprine, cyclosporine, dapsone, mycophenolate mofetil, and acitretin can be used. Systemic steroids are usually not advised due to risk of triggering pustular psoriasis.[3]

CONCLUSION

So far, only few cases of BP occurring concomitantly with psoriasis vulgaris have been reported in literature; hence, we are reporting this case for its rarity.

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Case report

Familial Disseminated Superficial Actinic Porokeratosis

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Abstract

Porokeratosis is a disorder of keratinization resulting from abnormal clonal expansion of keratinocytes. It may be sporadic or familial with autosomal dominant pattern of inheritance with variable penetrance. Lesions start as papules which develop into annular plaques with thin, thread like elevated rim. Diagnosis is confirmed by histopathological examination of pathognomonic Coronoid lamella. Here, we are reporting a familial case of disseminated superficial actinic porokeratosis in a mother and daughter.

Key words: Coronoid lamella, Familial, Parakeratosis, Porokeratosis

INTRODUCTION

Porokeratosis is a rare disorder of keratinization resulting from clonal expansion of keratinocytes characterized by well-defined plaque with hyperkeratotic ridges. It may be sporadic or familial with autosomal dominant pattern of inheritance with variable penetrance.[1] Exact pathogenesis is unclear, possible theories of pathogenesis include premature apoptosis of keratinocytes, reduced keratinocytic expression of filaggrin, and loricrin. In disseminated superficial actinic porokeratosis mutations in the SART3 and MeValonate Kinase genes on chromosome 12q24 normally play a role in keratinocyte differentiation and protect keratinocytes from apoptosis in response to damage from ultraviolet radiation (UV).[1,2] Risk factors include genetic inheritance, UV radiation and immunosuppression. Lesions start as papules or plaques which develop into annular lesions with thin, thread like elevated rim. Diagnosis is confirmed by histopathological examination of lesion which shows the pathognomonic Coronoid lamella. Malignant change into squamous cell carcinoma may occur.

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CASE REPORT

A 50-year-old female presented with complaints of asymptomatic skin lesions over face, chest, back, and right forearm for past 35 years. Initially, lesions started over face which gradually progressed to involve upper chest, right forearm, and back. History of similar lesions was present in her two brothers, sister, and her daughter. On examination, multiple well-defined annular plaques of varying size ranging from 1 × 1 cm to 2 × 2 cm present over face, upper chest [Figure 1a-c], right forearm, back [Figure 1d-f] with central atrophy and peripheral raised hyperpigmented furrowed margins. Oral mucosa, palms, and soles and genitals were normal.

Her 27-year-old daughter, presented with complaints of asymptomatic skin lesions over face for past 10 years. She is a known case of hypothyroidism on treatment. On examination multiple well-defined annular plaques of sizes ranging from 0.5 × 0.5 mm to 1 × 1 cm with central atrophy and peripheral raised hyperpigmented furrowed margins were present over face, scattered over forehead, and around eyes and cheeks [Figure 2a-c].

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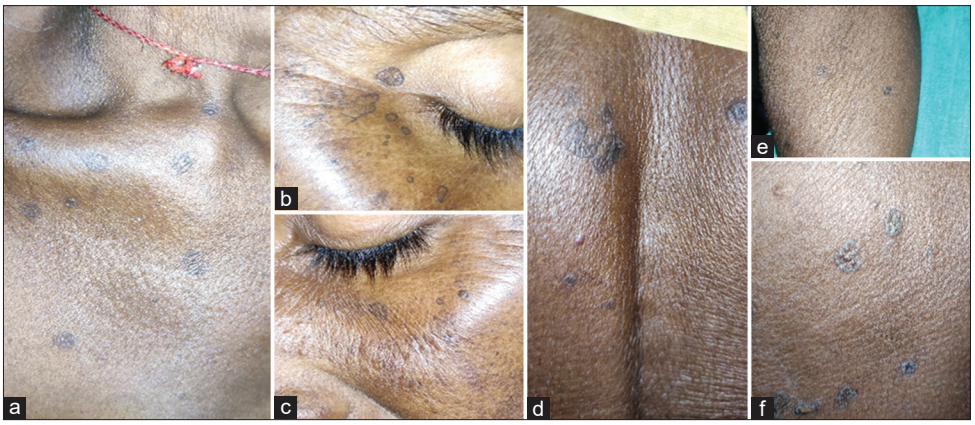

Figure 1: (a-c) Multiple plaques with central atrophy and peripheral hyperpigmented raised furrowed margin in the upper chest, right and left side of face in mother, (d-f) Multiple plaques with central atrophy and peripheral hyperpigmented raised furrowed margin in back and left forearm in mother

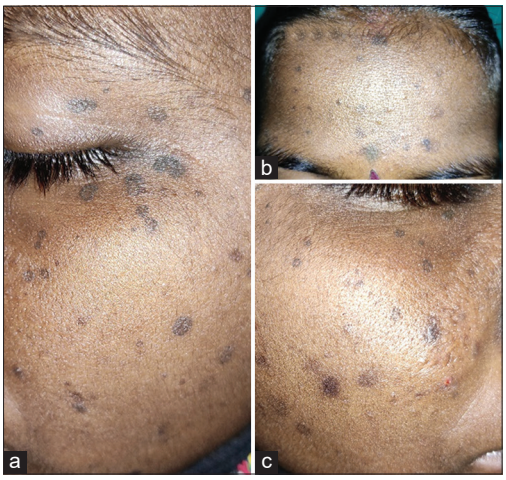

Figure 2: (a-c) Multiple plaques with central atrophy and peripheral hyperpigmented raised furrowed margin in forehead, bilateral cheeks in daughter

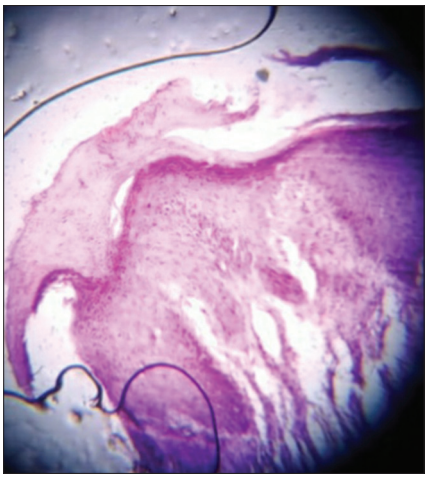

Figure 3: Hyperkeratosis, epidermal invagination filled with parakeratotic keratinocytes (coronoid lamella)

Histopathological examination of margin of lesions in both cases shows hyperkeratosis, epidermal invagination filled with thin column of tightly packed parakeratotic keratinocytes called coronoid lamella [Figure 3].

On the basis of history, clinical and histopathological examination, diagnosis of disseminated superficial actinic porokeratosis in mother and daughter was made.

DISCUSSION

Mibelli described classical porokeratosis in 1893. The lesions of porokeratosis results from peripheral expansion of abnormal, mutant clone of epidermal keratinocytes. Clinically, it is classified into localized and disseminated forms. Localized forms include porokeratosis of Mibelli, linear porokeratosis, punctate palmoplantar porokeratosis, perianal and genital porokeratosis. Disseminated forms include disseminated superficial porokeratosis, disseminated superficial actinic porokeratosis, systematized linear porokeratosis, and disseminated palmoplantar porokeratosis. Other unusual and rare forms include porokeratosis developing in gluteal region – porokeratosis ptychotropica, reticular and follicular variants. It may sometimes resemble punctate keratoderma, Darier disease, Cowden disease, and Arsenical keratosis.[3]

Malignant change is rare, if occurs squamous cell carcinoma is common, followed by Bowen's disease, basal cell carcinoma, and diffuse large B cell lymphoma.[4]

Histologically, it is characterized by coronoid lamella-thin column of tightly packed parakeratotic keratinocytes. Underlying granular layer is absent or attenuated. Dyskeratotic keratinocytes are present at the base of coronoid lamella.

Treatment options depend on the size and site of the lesions and include cryotherapy, topical 5-fluorouracil, topical imiquimod, topical Vitamin D analog, curettage, cautery, photodynamic therapy, and carbon dioxide laser.[5] Oral retinoids such as isotretinoin and acitretin were tried with variable success.

Familial disseminated superficial actinic porokeratosis is reported less in Indian literature and hence we report this case.

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Case Report

Combined Approach for Management of Calculi in Ileal Conduit

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Abstract

Urinary stones after urinary diversion are more common than general population. Renal stones are best managed with ESWL. The struvite stones fragment easily. The dilated refluxing ureter facilitates passage of fragments. Obtaining an access for nephrolithotomy is difficult with risk of sepsis. Large stones require percutaneous nephrolithotomy. For persistent stones in ureter, not responding to medical management, ureteroscopy, and lithotripsy is required. Retrograde access in urinary diversion is challenging, due to difficulty in locating the neo-ureteric orifice. Even for experienced endourologist. The best approach will be a combined antegrade and retrograde access.

Key words: Calculi, ESWL, Ileal conduit, Percutaneous nephrolithotomy, Retrograde intrarenal surgery, Urinary diversion

INTRODUCTION

Patients on urinary diversion have higher incidence of urinary stones. Overall incidence of stones in urinary diversion is 3–43%.[1] Incidence in conduit is 11–12%.[2] For ureteric calculi up to 10 mm medical management preferred.[1] Irrespective of the diversion type, the main difficulty in ureteroscopy is in locating the neo-ureteric orifices.[1,3] Ureteroscopy, semi-rigid, or flexible may require a combined endoscopic access. Procedure begins by gaining antegrade access with ultrasound guided puncture. Re-puncturing can be done onto an appropriate calyx for passing a guide wire below. The guide wire from above is retrieved below in the conduit. Following the guide wire, the neo-ureteric orifice is identified and ureteroscopy done.

CASE REPORT

A 63-year-old male presented with complaints of pain right upper abdomen, on and off for 2 months. Fever with rigors was present for 10 days. A known patient of carcinoma bladder, radical cystectomy, and ileal conduit diversion done 1 year back elsewhere. The operative notes were not available. Plain CT KUB showed dilated right ureter with 10.1 by 6.4 mm calculus of HU 415 in the ureter 4–5 cm above the conduit. The left ureter was dilated but without stones. The right kidney showed multiple stones in all calyces. Largest was in the upper calyx of size 2 cm. The left kidney had a stone of size 8 mm in middle calyx. Total leukocyte count was 21,000, with neutrophil predominance. The serum creatinine was 2.8 mg. The electrolytes were normal. The patient was managed in ICU. Mild metabolic acidosis presents. Blood for culture taken and injection meropenem started. Patient taken up for procedure after 18–24 h. Under regional anesthesia in supine position scopy through the conduit with 8-9.8 F storz semi-rigid ureteroscope carried out. The ureteric openings we are not identified. Patient changed to prone position, using ultrasound right middle calyx targeted and punctured with 18 G/21 cm two – part needle. Under C-arm diluted contrast injected slowly and pyelogram taken. The right upper ureter was dilated, ureteric calculus seen as a filling defect above the conduit, partially obstructing the lumen. A 0.035 terumo guide wire was passed across into the conduit and ante-grade stenting (6 F) done. The patient recovered well after the procedure and shifted to the ward after 2 days. Discharged after one more day in ward. He was on appropriate antibiotics, culture was *Escherichia coli* with significant colony counts. Silodosin given for 4 weeks. Repeat CT KUB taken [Figure 1a and b]. The ureteric calculus was in the same position. Ureteroscopy was decided. Under general anesthesia and supine position loopogram done [Figure 1c].

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A bit redundant conduit with Bricker anastomosis made out. Both the ureters were dilated and refluxing.

Using 8-9.8 F semi rigid ureteroscope scopy into conduit done and advanced along the side of the stent into the ureter. The ureteric calculus broken using storz Holmium-Yag LASER with medium fiber with setting 0.5 energy, 20 htz frequency, and 10 watts power. The stone was soft and easily broken. A 0.035 terumo guide wire passed into the pelvis. Storz Flex X 2 flexi scope was back loaded onto the guide wire to prevent buckling of scope. The scope was advanced into the renal pelvis under endovision. Stones in the calyces were broken with small fiber with same LASER settings [Figure 1e and f]. A stent was placed [Figure 1d]. After 8 weeks repeat CT KUB taken. There was complete stone clearance on the right side. The left renal calculus was present. The DJ stent removed. The serum creatinine was 2.0 mg/dl. The patient is on follow-up for 8 months. Three monthly USG KUB and serum creatinine were done. Serum creatinine is 2.2 mg on last follow-up. Monthly urine culture was done. He was on nitrofurantoin prophylaxis for 3 months. He takes Auxisoda two tablets 3 times a day.

DISCUSSION

Ureteroscopy was done as the stone still present after 4 weeks. As retrograde access is established, right intra-renal surgery was carried out with flexi ureteroscope. ESWL is contemplated on left side, if required. Common reasons for stone formation are refluxing urine with mucus, infection, hypercalciuria due to metabolic acidosis, hypocitraturia, hyperoxaluria, hyperphosphaturia, pouch stasis, and contact of urine with non-absorbable sutures and staples.[1,3] Lower incidence of stones in conduits may be due to absence of urinary stasis. Infection may be the important reason as most of the stones are struvite (63.5%).[2] Stones are common in the kidneys as well as the pouch.[1] Management of struvite stone involves appropriate antibiotic therapy before, during, and after surgery.

Antibiotic prophylaxis must be considered for stone prevention. In patients with conduits, the most common colonizers were skin flora, *Streptococcus*, and *Staphylococcus epidermidis*.[1] In pouch most common were *E. coli, Enterococcus faecalis, Enterococcus faecium*, and *Proteus mirabilis*.[1] The upper tracts are easily colonized, because of refluxing ureters. For renal calculi up to 2 cm ESWL, except for larger stones is preferred to percutaneous nephrolithotomy. ESWL Preffered to PCNL because of difficulty in access and increased risk of sepsis, due to bacterial colonisation.[1,4] Flexible ureteroscopy can be technically challenging in patients with urinary diversions. Difficulty is seen more in pouch than in conduits. The redundant conduit or a large cavity as in a pouch causes buckling of the scope. Buckling can prevent scope advancement and decreases the deflectability of the tip. Follow-up is needed to detect early stone recurrence.[1] The risk of new stone formation after 5 years is 50-63%.[2] Risk of stone formation is even more in patients with persistent bacteriuria.[5]

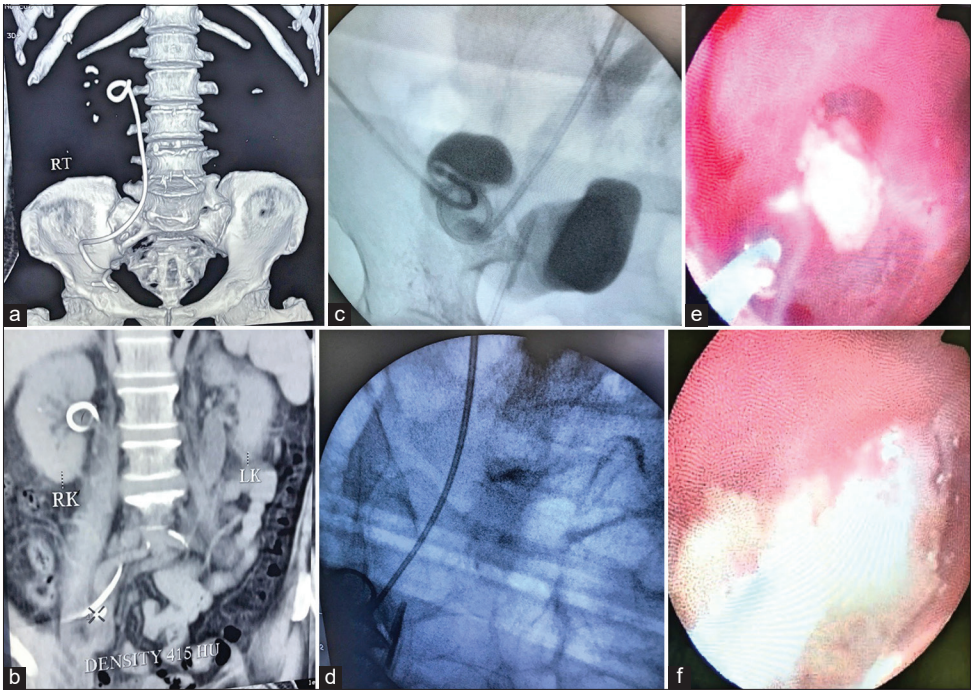

Figure 1: CT KUB, Pouchogram, Endoscopic view of RIRS

CONCLUSION

Ureteroscopy can be effectively done by combined endoscopic approach for management of stones in a urinary diversion.

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Case Report

Multiple Myeloma Presenting as a Maxillary Gingival Mass in Elderly Female

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Abstract

We report a case of multiple myeloma in elderly female, wherein diagnosis was arrived at after careful history taking and examination with series of investigations. This case is of significance since oral manifestations are uncommon as first manifestation of the disease and even rarer to occur in maxilla.

Key words: Bence Jones protein, Jaw, Myeloma, Oral

INTRODUCTION

Multiple myeloma (MM) is a malignant, multifocal malignancy of plasma cell origin which comprises 1% of all malignancies and 10–15% of hematologic malignancies.[1-3] It is characterized by abnormal clonal proliferation of plasma cells in bone marrow. It occurs between the 4th and 7th decades of life and is more seen in males as compared to females.[3] The clinical manifestations commonly seen are bone pain, anemia, fatigue, and affected areas involve skull, spine, pelvis, vertebrae, and hip.[4,5] Maxillofacial lesions are although not rare but are seldom seen as primary manifestation or early sign of disease. These lesions are seen in posterior segments of jaw being more common in mandible than maxilla. Patients with maxillofacial lesions present as ulceration, unhealed socket, paresthesia, tooth mobility, or gingival bleeding.

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Here, we present a case of MM in a 60-year-old female with oral manifestations as the primary manifestation of the disease and affecting maxilla which is a rare site of involvement. Through this case report, we would like to highlight the role of careful history taking, examination, and sequential investigations, leading up to timely diagnosis and management.

CASE REPORT

A 60-year-old female reported to the Department of Oral Medicine and Radiology with chief complaint of swelling in the right upper back tooth region for the past 2 months. She also complained of difficulty in swallowing and feeling of heaviness over the upper lip and right side of face. On eliciting history, the patient told that she had mobility of teeth in upper right quadrant posteriorly and underwent sequential extraction 5 months back of tooth no. 14, 15, 16, and 17. The patient started noticing a swelling at the extraction site for the past 2 months which was initially of a size of pea and progressed to the present size accompanied with pain in the region. The pain was dull, constant, localized in nature and was relived on taking anti-inflammatory drugs.

Medical history was positive for Type 2 diabetes mellitus for which she was on medications and active tuberculosis

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for which she was on antitubercular treatment for the past 4 months. No other family member was having any positive history. Personal history revealed the habit of paan chewing 2–3 times a day for 2 years and she had quit the habit 1 year back. General physical examination revealed an otherwise healthy female with moderate built, normal gait.

Extraoral examination showed no evidence of swelling; however, tenderness was present on palpation in the right zygomaticomaxillary region with overlying skin being normal in color, texture, and temperature. The right submandibular lymph node was palpable, 1 × 1 cm in size, firm in consistency, mobile, and tender on palpation. Intraorally, a soft-tissue growth of size 4 × 5 cm was present which was anteroposteriorly extending form distal end of 13 to the right maxillary tuberosity region and laterally obliterating the right maxillary buccal vestibule to medially approximately 0.5 cm away from midline of palate [Figure 1a]. It was soft to firm in consistency, sessile, non-pulsatile, slightly compressible, and ulcerated overlying mucosal surface with yellowish-white pseudomembranous slough due to impingement of opposing attrited tooth 46 [Figure 1b]. In the same region, teeth missing were 14, 15, 16, and 17 with Grade II mobility of 13 and an ill-fitting fixed prosthesis in relation to 12, 11, 21, and 22. Ill-fitting prosthesis was removed and tooth 13 was extracted. Subsequently, our differential diagnosis comprised secondary tuberculosis of oral cavity, malignant ameloblastoma, maxillary sinus malignancy, intraosseous carcinoma, osteosarcoma, and metastatic tumor. As the patient was on anti-tubercular therapy, hence, secondary tuberculosis involving oral cavity was considered as the first differential diagnosis.

A series of investigations were undertaken to arrive at a definite diagnosis keeping the above differential diagnosis in mind.

1) Maxillary occlusal view: It showed an ill-defined radiolucency involving the right hard palate not crossing the midline with severe bone loss mesial and distal to 13 [Figure 2a]. The panoramic radiograph revealed ill-defined radiolucency in the right maxillary region in relation to 13, 14, and 15 extending upward in maxillary sinus region [Figure 2b].
2) Contrast-enhanced computerized tomography (CECT): Spiral axial scans of the maxilla-mandibular region were obtained on multidetector computed tomography scanner followed by multiplanar reformats. It revealed the evidence of heterogeneously enhancing soft-tissue mass lesion of 5 × 5 × 4.5 cm in size involving the right hard palate and alveolar process of maxilla with bony destruction. The lesion was seen to extend into the right maxillary sinus, nasal cavity, superiorly the lesion was causing erosion of floor of the right orbit abutting the right inferior rectus muscle, infratemporal fossae causing thinning of pterygoid plates [Figures 2c-e]. Few subcentimetric bilateral level Ib, II lymph nodes were seen. Considering a short duration of history, maxillary location, soft consistency, numbness in same region, and destructive osteolytic lesion on radiographs suggested malignant neoplasm of different origin.
3) Hematological examination: Hemoglobin – 10.2 g/dl, total leukocyte count – 8700 mm^{-3}, differential leukocyte count – (neutrophils: 55.9%, lymphocytes: 33.3%, monocytes: 8.3%, and eosinophils: 2.4%), platelet count – 327,000 mm^{-3}, erythrocyte sedimentation rate – 40 mm/h.
4) Incisional biopsy of oral lesion: An incisional biopsy was performed and a 1.2 × 0.6 × 1 cm mass was incised from intraoral lesion under local anesthesia and was sent for histopathological examination. Lesional tissue revealed sheets of closely packed abundant mature plasma cells with few immature large cells. These cells showed round, ovoid, and angulated appearance of nuclei with the presence of chromatin clumping in a checkerboard and cartwheel pattern. The connective tissue stroma surrounding lesional tissue was loosely textured to collagenous in nature. The overall features were suggestive of plasmacytoma [Figures 3a and b]. Immunohistochemistry showed immunoreactivity for light chain lambda tumor marker suggestive of monoclonality [Figures 3c and d].
5) Bone marrow aspiration: Bone marrow aspirate and imprint smears were diluted with peripheral blood, occasional cellular marrow fragments entrapped in blood clot were seen. Myeloid-to-erythroid ratio was 3.5:1. Erythroid reaction was normoblastic with occasional micronormoblasts. Myeloid maturation series revealed mild increase in eosinophilic precursors as 8%. Megakaryocytes were adequate and functional. Plasma cells constituted 8% of marrow nucleated cells [Figures 4a-d]. Overall impression was suggestive of plasmacytoma.

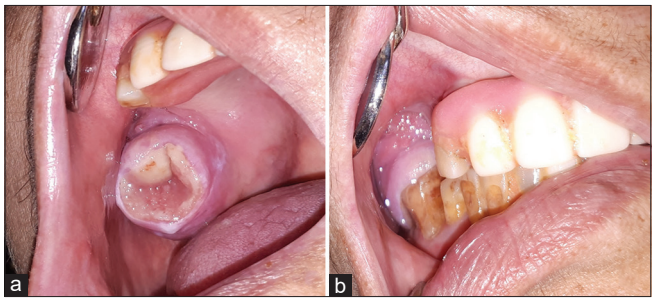

Figure 1: (a) Intraoral photograph showing soft-tissue growth of size 4 × 5 cm extending form distal end of 13 to the right maxillary tuberosity region, (b) intraoral photograph showing opposing tooth 46 impinging on the occlusal surface of the soft-tissue growth in maxillary region

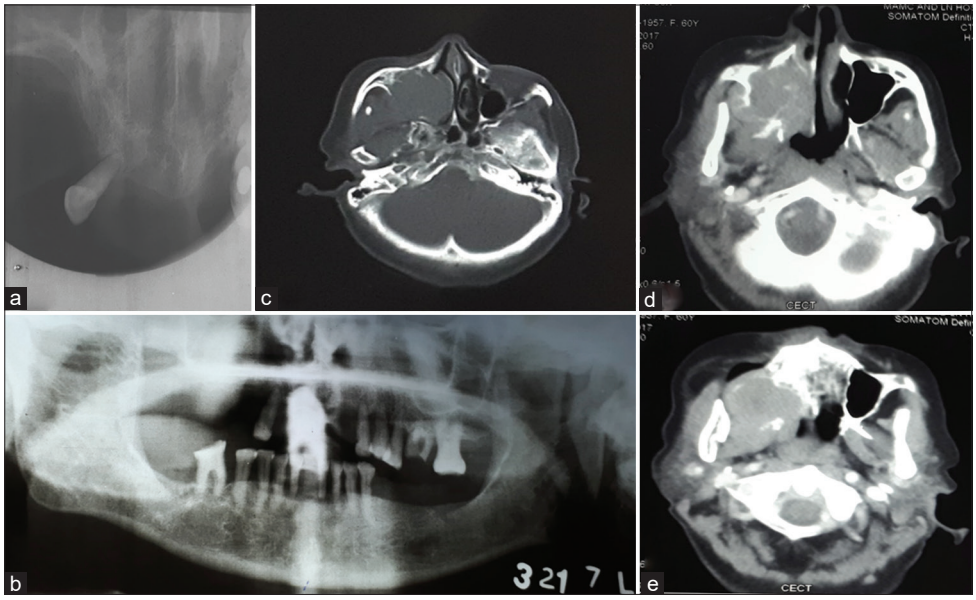

Figure 2: (a) Maxillary occlusal radiograph showing ill-defined radiolucency with soft-tissue density involving the right hard palate with severe bone loss mesial and distal to 13, (b) panoramic radiograph showing ill-defined radiolucency in the right maxillary region extending upwards in maxillary sinus region, (c-e) axial contrast-enhanced computerized tomography sections showing heterogeneously enhancing soft-tissue mass lesion of 5 × 5 × 4.5 cm involving right hard palate and alveolar process of maxilla extending into the right maxillary sinus, nasal cavity, and infratemporal fossae causing thinning of pterygoid plates

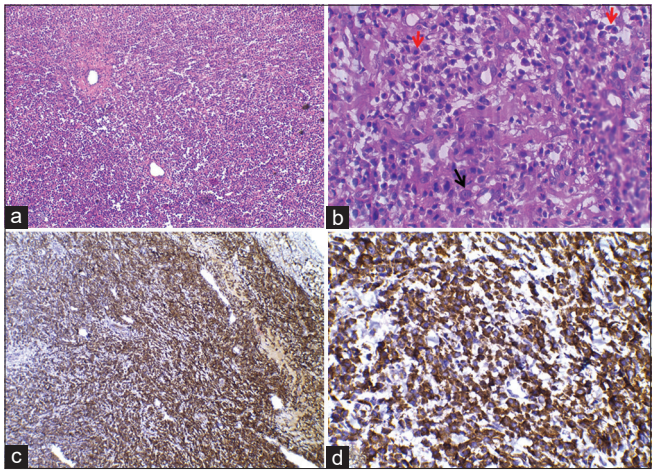

Figure 3: (a) Histological microphotograph (at 200×) of oral lesion showing sheets of closely packed abundant plasma cells, (b) histological microphotograph (at 400×) of oral lesion showing mature plasma cells (shown by red arrows) and immature plasma cell (shown by black arrow), (c and d) immunohistochemical microphotograph (at 200× and 400×) of oral lesion showing immunoreactivity for light chain lambda tumor marker

6) Bone marrow biopsy: H and E stained bone marrow biopsy showed many bony trabeculae with intratrabecular spaces enclosing hypocellular marrow. It revealed hematopoietic cells of all lineages with focal interstitial and mild increase in plasma cells which were <10% [Figure 5a]. Erythroid series showed normoblastic erythroid reaction. Myeloid series showed normal maturation with mild increase in eosinophils. Megakaryocytes were seen and adequate in number. There were CD38 positive plasma cells on immunohistochemical staining [Figure 5b].
7) Skeletal survey: Anteroposterior (AP) and lateral skull radiograph showed multiple, well-defined punched out lytic lesions in bony calvaria [Figure 6a]. Posteroanterior (PA) chest radiograph showed a lytic lesion in medial end of the right clavicle and fibrotic opacities in bilateral upper zone of lungs [Figure 6b]. Lateral radiographic view of cervical spine revealed straightening of cervical spine with marginal osteophytes at multiple levels [Figure 6c]. AP and lateral radiographic views of dorsolumbar and lumbosacral spine showed diffuse osteopenia [Figures 5e and 6d]. Radiograph of bilateral hip and pelvis was normal. CECT chest revealed well-defined soft-tissue lesion in the left upper lobe with few nodules having irregular margins in the right upper lobe, left upper, and lower lobe [Figure 6f], a lytic lesion with associated soft tissue in the right 4th rib and spinous process of D2 vertebra with epidural extension [Figure 6g].
8) Serological and immunological examination: Serum electrophoresis was negative for M spike. Urinary Bence Jones proteins were negative. Liver function and kidney function tests were within normal limits. Serum β_2 microglobulin level was 3524 ng/ml which was significantly raised (normal limit: 609–2366 ng/ml). Serum kappa free light chain and lambda free light chain were significantly increased, that is, 30.60 mg/l (normal limit: 3.30–19.40 mg/l) and 995 mg/l (normal limit: 5.71–26.30 mg/l), respectively.

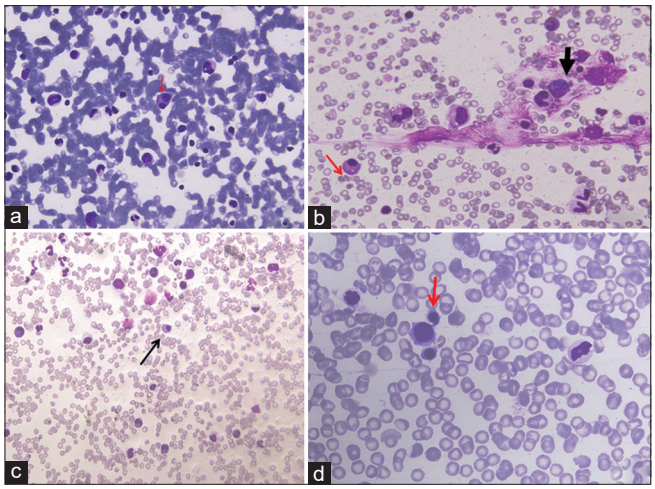

Figure 4: (a) Histological microphotograph (at 400×) of bone marrow aspirate showing binucleated plasma cell (shown by an arrow), (b) histological microphotograph (at 400×) of bone marrow aspirate showing plasma cell (shown by an arrow), (c) histological microphotograph (at 600×) of bone marrow aspirate showing plasma cell (shown by red arrow) and eosinophilic precursor (shown by black arrow), (d) histological microphotograph of bone marrow aspirate showing macronormoblastic erythroid precursor (shown by an arrow)

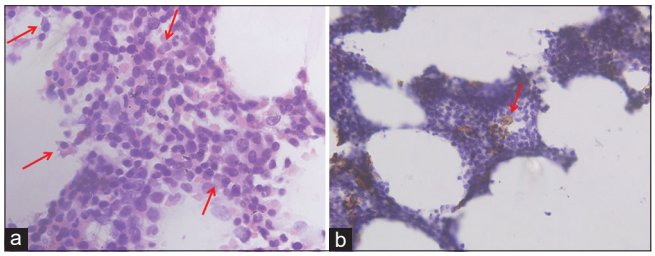

Figure 5: (a) Histological microphotograph (at 400×) of bone marrow biopsy showing plasma cells (shown by arrows), (b) microphotograph (at 400×) of bone marrow biopsy showing immunohistochemical expression of CD 38-positive plasma cells (shown by an arrow)

Based on all investigations and criteria for diagnosis of plasma cell disorders, a final diagnosis of MM was made. The uniqueness of the present case highlights that how a maxillary swelling with no other systemic symptoms turned out to be MM on subjecting to a series of investigations.

Based on the diagnosis of MM and considering the age of patient, (RVD) chemotherapy regimen was started which included tablet lenalidomide 25 mg (once a day from day 1 to day 21), injection bortezomib 1.3 mg/m^2 (2 mg intravenously over 2 min at day 1, day 4, day 8, and day 11), and tablet dexamethasone 40 mg (once a day at day1, day 8, and day 18). The patient underwent 6 cycles at an interval of 4 weeks and responded well with no complications. The patient has shown considerable improvement with almost complete resolution [Figure 7].

DISCUSSION

MM is the prototype of malignant monoclonal gammopathies with the cell of origin being the B-cell in late stage of development process occurring primarily in the bone marrow. MM is characterized by chronic, progressive, clonal neoplastic proliferation of abnormal plasma cells which secretes monoclonal immunoglobulins in the serum, often known as "M" or myeloma proteins.[1,2] It accounts for 1% of all the cancers and approximately 10% of all hematologic malignancies.[3,4] It involves a complex, multistep process, wherein healthy plasma cells transform into malignant myeloma cell resulting in production of abnormal immunoglobulins or M proteins. In normal condition, development of B-cell involves a sequence of conformational changes in DNA leading to the formation of plasmablasts (immature plasma cells) and eventually specific immunoglobulins secreting plasma cells. However, in MM, there is neoplastic transformation of B-cell in late stages of development leading to clonal proliferation of abnormal plasma cells which in most of the cases is characterized by pathological chromosomal translocation involving immunoglobulin heavy chain switch region.[5] Emerging researches have also proposed that dysregulated cyclins are responsible for uncontrolled proliferation of abnormal cells.[6]

The common age group to be affected range from 50 to 80 years with means age being 60 years with male predominance.[7] The most common skeletal sites to be involved are pelvis, skull, spine, ribs, and femoral and humeral shafts.[5] In case of jaw bones, mandible is more commonly involved than maxilla and the attributed reason for this is due to lower content of marrow space in mandible although the present case showed maxillary involvement. Bruce and Royer[8] and Miller *et al.*[9] had found the involvement of jaws in 20–30% of the cases only. Literature has shown that maxillary involvement is even rarer than mandible. Lambertenghi-Deliliers *et al.*[10] said that out of 193 cases, none of the case showed maxillary involvement, Pisano *et al.*[11] concluded saying that 4 out of 13 cases had maxillary involvement and Lae *et al.*[12] reported the involvement of maxilla in 7 out of 33 cases. The clinical manifestations are due to the expansion of abnormal plasma cells in bone marrow which secretes monoclonal light chain or heavy chain immunoglobulin, Bence-Jones proteins, and osteoclast activating factors. The most common clinical manifestations include renal failure, bone pain, fatigue, anemia, hypercalcemia, and infectious diseases, however, no such signs and symptoms were present in the present case except anemia.[13,14] The initial sign of MM in the form of oral and maxillofacial manifestations is a very rare presentation with an incidence of 2–70%.[15,16] The oral manifestations of MM resembles the features of that of malignancy such as pain, paresthesia,

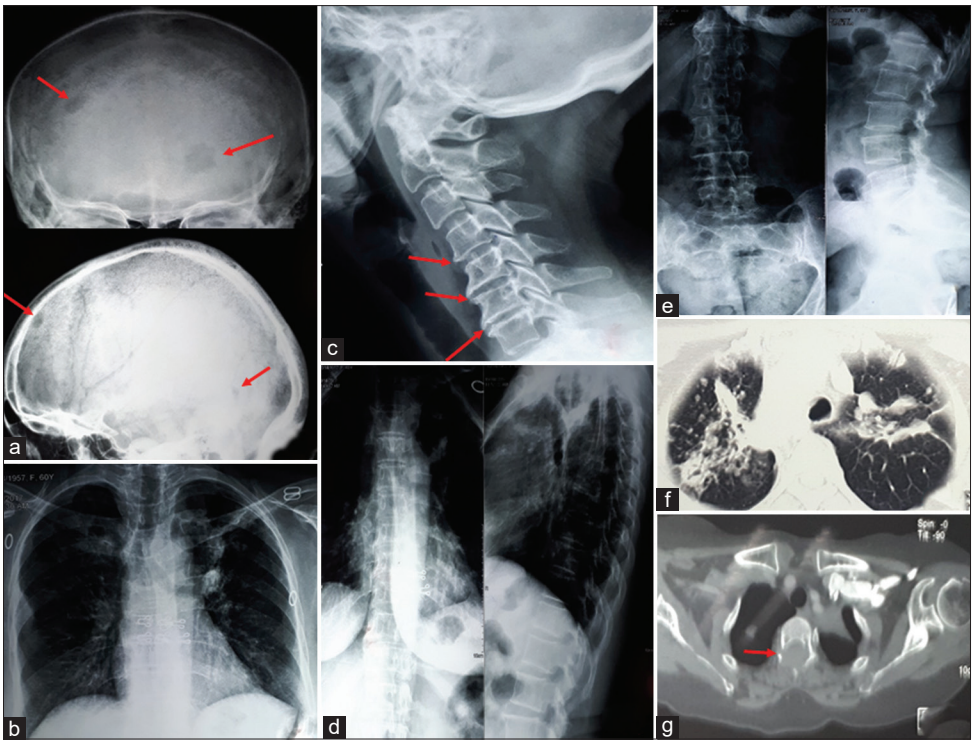

Figure 6: (a) Anteroposterior (AP) and lateral view of skull radiograph showing multiple, well-defined punched out lytic lesions in bony calvaria (shown by arrows), (b) posteroanterior chest radiograph showing a lytic lesion in medial end of the right clavicle and fibrotic opacities in bilateral upper zone of lungs, (c) lateral view of cervical spine radiograph straightening of cervical spine with marginal osteophytes at multiple levels (shown by arrows), (d and e) AP and lateral radiographic views of dorsolumbar and lumbosacral spine showing diffuse osteopenia, (f) axial section of contrast-enhanced computerized tomography (CECT) chest showing well-defined soft-tissue lesion in the left upper lobe with few nodules having irregular margins in the right upper lobe, left upper, and lower lobe, (g) CECT axial section showing a lytic lesion with associated soft tissue in the right 4th rib and spinous process of D2 vertebra with epidural extension (shown by an arrow)

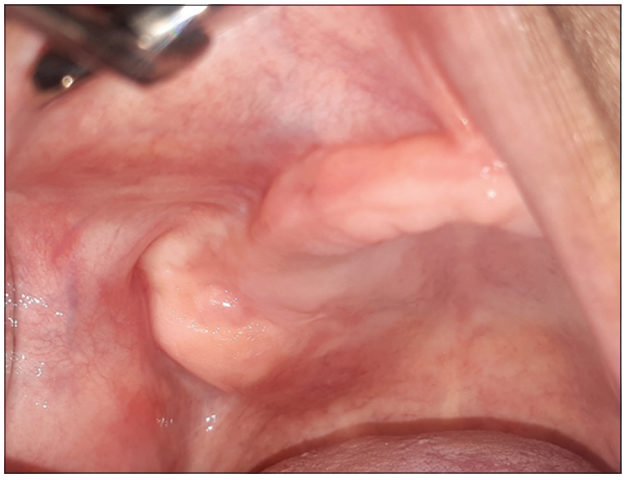

Figure 7: Intraoral photograph showing almost complete resolution of the maxillary lesion after 6 cycles of chemotherapy at an interval of 4 weeks

mucosal ulcerations, swelling, soft-tissue mass, tooth mobility and migration, and pathological fractures.[5]

The series of investigations are required to arrive at definitive diagnosis of MM which involves workup including histopathological confirmation of proliferation of malignant plasma cells, hematological examination, biochemical and immunological examination, urine analysis, bone marrow aspirate, and skeletal survey.[17] When MM is suspected, it is necessary to evaluate the patient for the presence of M proteins using a combination of tests that should include a serum protein electrophoresis, serum immunofixation, and the serum free light chain (FLC) assay.[18] Approximately 2% of patients with MM have true non-secretory disease and have no evidence of an M protein on any of the above studies.[18] The revised International Myeloma Working Group criteria for the diagnosis of MM are ≥10% clonal bone marrow plasma cells or a biopsy-proven plasmacytoma plus evidence of one or more MM defining events: CRAB (hypercalcemia, renal failure, anemia, or lytic bone lesions) features felt related to the plasma cell disorder, bone marrow clonal plasmacytosis ≥60%, serum involved/uninvolved FLC ratio ≥100 (provided involved FLC is ≥100 mg/L), or >1 focal lesion on magnetic resonance imaging.[18] As per the above-mentioned criteria for the diagnosis of MM, the present case fulfilled the biopsy-proven plasmacytoma, anemia, lytic bone lesions, and increased FLC.

Radiographic presentation of MM is commonly osteolytic lesions with irregular, non-corticated margins, and multiple

punched out radiolucencies which could be attributed to infiltration of bone by malignant plasma cells secreting various bone resorbing factors. The four different radiological appearances of bony destruction caused by malignant plasma cells are as follows: Type 1: Solitary type (similar to bone cyst); Type 2: Multiple osteolytic lesions without marginal sclerosis (a) central type and (b) peripheral type; Type 3: Diffuse osteoporosis with generalized involvement; and Type 4: Diffuse osteosclerosis.[19] In the presence case, skull, clavicle, rib, and D2 vertebra showed Type 2 variety, and dorsolumbar and lumbosacral spine showed Type 3 form. Although skeletal conventional plain radiographs have vital contribution toward the assessment of bony involvement, low-dose whole-body CECT, PET/CT, and MRI imaging are more sensitive and should be advised when no changes are observed on routine radiographs, dilemma about the true extent of the disease as well as to assess treatment response and monitoring.

Treatment of MM involves mainly radiation therapy, chemotherapy, and autologous stem cell transplantation. The treatment plan and prognosis is determined by risk stratification through Revised International Staging System which defines three stages on the basis of serum albumin, serum β_2 microglobulin, and high-risk cytogenetics and serum lactate dehydrogenase.[20] Overall survival rate in MM has improved significantly with the emergence of thalidomide, bortezomib, and lenalidomide, and more recently, carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, and daratumumab have been approved by the Food and Drug Administration (FDA) for the treatment of relapsed MM, and promise to improve outcomes further and several combinations of these drugs have been used in the management of MM successfully.[18]

CONCLUSION

A case of MM has been reported wherein primary manifestation in the form of soft-tissue mass in maxilla was present which is a very unusual and rare presentation and no other systemic symptoms were reported. However, we arrived at the conclusive diagnosis of MM after following proper diagnostic protocol through series of investigations along with ruling out other disorders and therefore able to deliver the apt treatment. Hence, it is suggested with reinforcing the role of clinicians in the appropriate workup, early diagnosis, and timely management of such systemic conditions and thus reducing mortality and morbidity in such cases.

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Review Article

Endometriosis-associated Infertility: Treatment Modalities

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Abstract

Endometriosis is a common chronic inflammatory condition, which severely affects women of reproductive age. It is defined as the implantation of endometrial glands and stroma outside the uterine cavity. These ectopic endometriotic lesions may be asymptomatic, but most commonly, women present with pelvic pain, adnexal mass(es), dyspareunia, infertility, dyschezia, dysuria, and rarely dyspnea, thus adversely affecting women's overall health. It not only hampers their quality of life but also has a deleterious effect on their reproductive ability and personal relationship. Endometriosis is a multifactorial disease and is known to affect fertility but does not totally prevent conception. Management of endometriosis lies whether the complaint is about pain or about infertility. Different treatment modalities have been employed to treat endometriosis, starting from conservative to surgical management. This literature review will highlight on how endometriosis affects fertility and the various treatment options available to treat women presenting with endometriosis-associated with infertility.

Key words: Anti-Mullerian hormone, Dysmenorrhea, Dyspareunia, Endometriosis, *In vitro* fertilization, Infertility

INTRODUCTION

Endometriosis is an estrogen dependent gynecological disease with a prevalence of 10-15% that affects women of reproductive age.[1] The true prevalence is difficult to quantify as wide ranges have been reported in the literature. Studies have suggested that about 25–50% of infertile women are found to have endometriosis, and 30–50% of women with endometriosis are infertile.[2]

The prevalence of endometriosis has increased to as high as 25–50% in infertile women[3] which infers that it has a negative effect on woman's child-bearing ability.

Endometriosis is one of the most common gynecological disease presenting to the outpatient gynecology clinic. It is defined as the presence of endometrial glands or endometrial tissues outside the uterine cavity in ectopic locations. The most common site of these endometrial implants are as follows: Ovaries being the most frequently involved, followed by anterior/posterior cul-de-sac, broad ligament, uterosacral ligament, uterus, fallopian tubes, sigmoid colon, and appendix. However, the presence of extra-peritoneal ectopic endometrial tissues has also been reported in the literature such as lungs, diaphragm, upper abdomen, and the central nervous system.[4]

Endometriosis may present as variable clinical presentations, some women are asymptomatic, while others present with painful cyclic menstruation, chronic pelvic discomfort, painful sexual intercourse (dyspareunia), dyschezia, and subfertility, which severely hamper the quality of life in these women. Endometriosis is a histological diagnosis. Laparoscopy and biopsy of the endometriotic implant are considered as the gold standard for the definitive diagnosis of endometriosis.[5]

The treatment in these patients depends upon the presenting complaint, severity of the disease, and the desire to preserve fertility.

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Conservative treatment includes gonadotropin-releasing hormone analogs, oral contraceptive pills, prostaglandins (PG), aromatase inhibitors (AIs), and non-steroidal anti-inflammatory drugs (NSAIDs). Surgical management is indicated for pain alleviation in advanced cases of endometriosis[6] and also for releasing pelvic adhesions that may impact reproductive functionality.

ETIOLOGY OF ENDOMETRIOSIS

The pathogenesis of endometriosis is multifactorial. It is a benign but a progress and an aggressive disease. There are several theories hypothesized explaining the pathogenesis of endometriosis, but no single theory explains all the disease manifestations. One of the most popular and accepted theory proposed by Sampson is the theory of retrograde menstruation. In his theory, he hypothesized that the backward flow of endometrial cells shed during causes pelvic endometriosis.[7] The transfer of these progenitor cells from the uterine endometrium to ectopic location results in implantation of these tissues into the peritoneum, ovaries, fallopian tube, and cul de sac, which then grows in the presence of cyclic hormones resulting in a chronic inflammatory reaction resulting in pain, pelvic adhesions, and infertility issues.[8,9]

Another theory by Halban, 1925, proposed that the spread of endometrial cells to extra-peritoneal and distant extra-pelvic sites could be through the lymphatic channels and the vascular system. Hematogenous spread of the endometrial cells is best explained by this theory in cases of endometriosis of the lungs, forearm, and thighs.

Another contrasting theory by Meyer *et al.*, 1924 hypothesizes that endometriosis arises from the metaplasia of the coelomic epithelium. Majority of the female reproductive tract is derived from the Mullerian duct and the Mullerian duct is a derivative of coelomic epithelium.

This theory postulates that the coelomic epithelium is multipotent and has the ability to differentiate into different histological cell types. Endometriosis has also been reported to have found in prepubertal girls, women with an absent uterus and also in men, rarely.[10] These examples support this theory of coelomic metaplasia.

It is recently speculated that the survival of endometrial cells outside the uterine cavity is due to the overexpression of CD 147 which is an anti-apoptotic factor.[11] Due to the imbalance of pro and anti-apoptotic factors, endometrial cells stay in these ectopic locations.

Recent studies have also speculated that endometriosis could be due to bone marrow-derived stem cells.[12] A recent study identified the presence of chimerism in the endometrial cells of four women who underwent bone marrow transplants, thus suggesting that bone marrow-derived stem cells contributed to the overgrowth of the endometrium in these patients.[13]

Moreover, in contrast, molecules such as the fibroblast growth factor receptor have been over-expressed in ectopic locations causing these females to suffer from endometriosis. Studies have also demonstrated that in patients with post-surgery recurrence, there was overexpression of fibroblast growth factor receptor 1.[14]

Among the various endometriotic lesions, peritoneal lesions induce an inflammatory reaction which enables the activation of T helper cells. When the acute phase resolves, the process of chronic inflammation is carried by monocytes and macrophages, resulting in peritoneal adhesion and formation of new blood vessels (angiogenesis).

Endometriosis is an estrogen-dependent disease. During the luteal phase of a woman with a normal menstrual cycle, progesterone is secreted and in response to the progesterone, endometrium results in the transformation from proliferative to secretory phase. In a patient with endometriosis, a reduced response to progesterone is seen and hence estrogen aggravates the pathological process of inflammation and growth of the endometrial cells, thus causing the symptoms of endometriosis.[15]

CLINICAL MANIFESTATIONS

The most commonly presenting debilitating symptom in patients with endometriosis is pain. These women have typical symptoms of dysmenorrhea (painful menstruation), often starting with menarche. They also complain of dysuria (painful urination), dyspareunia (painful sexual intercourse), dyschezia (pain on defecation), chronic pelvic pain, and fatigue.[16] Studies show that endometriosis is strongly associated with infertility. As an estimation, 30–35% people with endometriosis are associated with infertility and vice versa.[17]

The mechanism explaining the link between endometriosis and infertility is poorly understood. It is believed that the endometrial implants cause major pelvic adhesions, thus impairing oocyte release from the ovary or inhibiting ovum transport due to tubal adhesions, thus negatively impacting fertility by decreasing fecundity in women with endometriosis.[17]

The initial evaluation for endometriosis in a patient is made by complete detailed history taking and physical examination, including the bimanual pelvic examination.

History and physical examination mostly yield a significant number of findings which are suggestive of endometriosis. On bimanual examination, dyspareunia, a fixed retroverted uterus, uterosacral ligament nodularity, deep infiltrating thick lesions appearing as nodules, and adnexal masses can easily be identified by palpation.

Tumor marker, like, CA-125 is usually raised in women with endometriosis; however, it should not be taken into consideration as they lack sensitivity and specificity.[18] Biomarkers obtained from the serum, plasma, and urine is of no clinical significance in these patients.[19] Ultrasound of the pelvis can help in identifying ovarian endometrioma but is a poor imaging modality in identifying peritoneal and extrapelvic implants. Upon comparison between transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI) pelvis in detecting deep rectosigmoidal and retrocervical endometriotic lesions, TVUS had a sensitivity of 98%, specificity of 100%, positive predictive value (PPV) of 100%, negative predictive value (NPV) of 98%, and accuracy of 99%. Whereas, MRI had sensitivity of 83%, specificity of 98%, PPV of 98%, NPV of 85%, and accuracy of 90%.[20] Transvaginal sonography (TVS) not only helps in detecting endometriotic lesions but also aids in reflecting adhesion and help in visualizing pelvic fluid on sonography. Several reviews have concluded that TVS can reliably detect endometriotic lesions in comparison to MRI.[20]

In cases of moderate to severe endometriosis, where the symptoms have not resolved in spite of undergoing medical management, laparoscopy is indicated.[21]

Laparoscopy is the gold standard in diagnosing and inspecting endometriotic lesions.

The definitive diagnosis should be made after confirming the positive laparoscopic findings with histopathology of the lesions to exclude any other cause.[22] However, laparoscopy should only be reserved only for the symptomatic patient who presents with pain secondary to adhesions or for treating stage III OR IV endometriosis.

TREATMENTS

Depending upon the age, severity, location, and desire for future fertility, treatment must be tailored for each patient, whether medical or surgical management is needed.

Medical Management of Endometriosis

NSAIDS

Ibuprofen, indomethacin, naproxen, suprofen, mefenamic acid, lexofenac, and diclofenac are some of the examples of NSAID's. They are used as the first line in treatment for pain alleviation in patients who present with dysmenorrhea. Their mechanism of action is by inhibiting cyclooxygenase, an enzyme that converts arachidonic acid into PG, prostacyclin, and thromboxanes. The thromboxanes play a major role in platelet adhesions. PG causes vasodilation and increases the temperature in the hypothalamus, thus causing pain.

NSAIDs inhibit this conversion and prevent the production of PG and thromboxanes. They are successfully used in treating patients with dysmenorrhea, menorrhagia, and pain associated with intrauterine devices (IUDs). They ameliorate menstrual pain by decreasing the level of PG F2 alpha in the endometrial cells. It also acts by decreasing the intrauterine pressure and menstrual blood loss. In a study comparing the effect of pain relief in a patient using NSAIDs versus acetaminophen, relief by NSAIDs was 80–85% and it was superior in achieving symptomatic relief in a patient with dysmenorrhea as compared to acetaminophen.[22]

Combined oral contraceptive pills (COCP)

The use of hormonal therapy for a period of minimum 6 months has shown to suppress and regulate ovarian hormonal imbalance. It has also aid in alleviating pain associated with endometriosis.[23] Studies have shown that there is a significant decrease in the size of endometriomas with the use of OCPs. This is mostly due to an increment in apoptotic rate in the endometrium which is ectopic and also there is downregulation of cell proliferation.[24] Continuous administration of COCPs has been proven to be more effective in ameliorating the symptoms of painful menstruation, reducing the size of endometriomas and pelvic pain in comparison to cyclic administration.[25] Studies have shown that the long-term use of cyclic OCPs for 3 years following surgical resection of endometriosis resulted in a decrease of recurrence rate of endometriosis by 50%.[26] Review by Vercellini *et al.* suggested that ovulation suppression is an important reason in preventing the recurrence of endometriomas. In addition to prescribing the drugs to the patient, potential side effect should also be kept in mind. The side effect of oral contraceptives includes bloating, weight gain, mood swings, increase in breakthrough bleeding, and increase in blood clot formation. There is also a decrease in libido. Hypoestrogenic state causes menopausal symptoms such as night sweats, hot flushes, vaginal dryness, and fatigue.

Progestins

Progestins are synthetic compounds that mimic the action of progesterone, they come in various concentrations, doses, and forms of administration such as oral administration, injectables, intrauterine administration, and subdermal implantation. The oral route drugs include

medroxyprogesterone acetate given 30–60 mg/day, dienogest (visanne) 2 mg/day, cyproterone acetate 10–12.5 mg/day, and norethisterone acetate (primolut N) 2.5–5 mg/day. Injectable, depot medroxyprogesterone acetate (Depo Provera) can be given in a dose of 50 mg/week intramuscularly. Subdermal implants (Implanon) are a single rod of 68 mg inserted subdermally in an outpatient setting using it is applicator by a trained nurse or a physician. This is effective for 3 years and must be replaced/removed after 3 years or whenever women desire fertility. IUD such as levonorgestrel intrauterine system (Mirena) contains 52 mg of levonorgestrel which can be placed into the uterus, also in an outpatient setting by a physician or a trained nurse. This can be used up to 5 years, but a follow-up transabdominal ultrasound every 12 months is recommended to check for its position if the women are unable to feel the thread.

Progestin works by ovulation suppression. It negatively inhibits the pulsatile effect of gonadotrophin-releasing hormone (GnRH) which further works by decreasing the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion from the pituitary hence resulting in ovarian suppression with a low level of ovarian steroids.[27] This long-standing hypoestrogenic state results in the transformation of ectopic endometrium which leads to atrophy, decidualization, and alteration in steroid receptor binding ligand in the endometrium.

Since endometrial foci consist of a very few progesterone receptors such as PR-β, which is undetectable, and PR-α, which is reduced. As a result, progestin causes downregulation in further synthesis of these receptors and acts by working on progesterone receptor expression and progesterone resistance. Progestin also alleviates the pain by suppressing the production of interleukin-8 (IL-8), tumor necrotic factor-α (TNF-α) induced nuclear factor-χ-β. It increases the production of nitric oxide. It also has a negative effect on angiogenesis which is (formation of new blood vessels) on the ectopic endometrium by suppressing the transcription of basic fibroblast growth factor, vascular endothelial growth factor, and cysteine-rich angiogenic inducer [CYR61]).[28] The side effect of progestin includes abnormal uterine bleeding, nausea, breast tenderness, fluid retention, and depression.

Androgen

The use of androgen creates a hyper-androgenic state by inhibiting FSH and the LH, which results in the atrophy of the endometriotic implants, thus useful in the treatment of dysmenorrhea. Danazol is an androgenic drug, one of its major reported side-effects includes hirsutism (excessive hair growth). Weight gain, vaginal spotting, voice change, acne, and muscle cramps are some of the other reversible adverse effects seen with this drug. With the hypoestrogenic effect of danazol, premenopausal symptoms such as hot flushes, amenorrhea, and vasomotor symptoms are noticed, but these are reversible with the cessation of the drug use. The recommended dose of danazol is 400 mg/day; the dosage can be increased till there is a cessation of menses.[29]

GnRH agonist

The GnRH agonists are among the most effective medications available to treat endometriosis. The side effects of GnRH agonists include menopausal-like symptoms such as vaginal dryness, hot flashes, and osteopenia.

They are believed to work by making an estrogen-deficient state starting immediately after 2 weeks of beginning the therapy. They work by increasing the release of GnRHs by triggering the pituitary to release FSH and LH, which result in a flare effect and negatively inhibits GnRH, that is, FSH and LH by downregulating them, resulting in a hypoestrogenic state.

Gelety *et al.* confirmed that the symptoms of the flare effect were exacerbated more in the follicular phase. Hence, it is advised to give GnRH agonist in the mid-luteal phase.[30] Furthermore, Meldrum *et al.* concluded that there was a rapid progressive pituitary suppression when GnRH is given in the beginning of mid-luteal phase.[31]

GnRH agonists are generally used to shrink the size of the endometrial implants; it is also used before surgeries to decrease the size of these implants and endometriomas; also, it helps to prevent the removal of excessive scar tissues.

Due to the hypoestrogenic state, women experience menopausal symptoms. The side effects of GnRH agonists include vaginal dryness, hot flashes, and osteopenia. Hence, the use of GnRH is limited to 12 months only. It is also recommended that add-back therapy be initiated after 6 months of GnRH agonist use if it was not started previously. Usually, progestins, the combination of progestins and estrogen, have been used for add-back therapy.[32] Loss of bone mineral density is reversible with the cessation of the GnRH agonists.

AIs

Aromatase inhibitors (AIs) works by supressing estrogen production in the ovarian and peripheral tissue. There are three generations of AIs, the first, the second (fadrozole and formestane), and the third generation (anastrozole and letrozole). The route of administration for the first and second is intramuscular injection. Third generation AI's can be administered orally. Amongst the three generations of Ais, the most potent is the third generation.

They increase the level of FSH in premenopausal women, thus mimicking a menopausal state. Adverse effect of it includes symptoms similar to postmenopausal state. Aromatase activity has been found in ectopic endometrial lesions as compared to the normal endometrium, ectopic endometrium lesions have estrogen sources, which converts them to PGE2 leading to additional growth of ectopic endometrial tissue. Therefore, AIs work by inhibiting this vicious cycle.[33] A study by Patwardhan *et al.* confirmed that AIs have a pain-controlling effect. It decreases the size of endometrial implants and improves the quality of life when combined with OCPs or GnRH-agonists.[34]

Surgical Treatment for Endometriosis

Surgery is indicated when medical treatment has failed. Severity of symptoms and the presence of large endometriomas may direct to provide surgical intervention sooner.

Laparoscopy or laparotomy is the choice in the management of patients with deep pelvic endometriosis, more specifically in patients with advanced-stage endometriosis. It includes removal of endometriotic lesion by excision, coagulation, ablation, interruption of nerve to alleviate pain, and restoration of the anatomy. Surgical option remains debatable in the early stage of the disease; however, it has shown to improve the symptoms and progression of the disease. In patients with ovarian endometrioma having a cyst >3 cm, technique of ablation and coagulation revealed lower chances of recurrence with dysmenorrhea and dyspareunia and the rate of cyst recurrence was diminished too.[35] Studies have shown that the recurrence of endometrial implants after endometrial ablation versus those women who did not undergo endometrial ablation was almost zero.

Moreover, after the ablation treatment, patients did not exhibit retrograde menstruation or ectopic endometriotic implants. This method not only helped in ameliorating the pain but also stood as an alternative to hysterectomy in women who wish to preserve future fertility.[36]

DISCUSSION

Endometriosis and Infertility

Despite several researches and studies, the exact correlation between endometriosis and infertility is unknown and this topic is very debatable. Several ideologies have been proposed to explain the relationship between the two, which includes abnormalities in endocrine and ovarian function, altered hormonal function of endometrium, impaired luteal phase defect or multiple LH surges, progesterone resistance, deleterious effect on spermatozoa, dysfunctional utero-tubal ability, anti-endometrial antibodies, pelvic adhesion, and fallopian tube inflammation due to peritubular adhesions, which can impede the patency of the tube and thus result in impaired oocyte pickup from the ovaries and diminished ovum transfer along the tube. Impaired folliculogenesis is also seen in this patient with endometriosis.[37]

In patients with ovarian endometriosis, cystectomy of endometriomas may result in a greater loss of ovarian reserve because the surgery involves the removal of a larger amount of ovarian stromal tissue to which these endometriotic lesions are adhered, this result in damage and decreased ovarian reserve.[38]

In women with chronic endometriosis, a decreased ovarian response is seen due to increased concentration of IL-1b, IL-8, IL-10, and TNF.

Elevated amount of cytokines, specifically IL-6 in the peritoneal fluid of these women, is also known to cause inhibition of sperm motility.[38,39] Embryo implantation is also affected by complex behavior of ectopic endometrial implants.

Due to these functional disorders of the endometrium, abnormal uterine contractions are seen in these patients.

For fertilization to occur, there has to be an optimal uterine cavity that enables sperm transportation to undergo capacitation in the ampulla of the fallopian tube to fertilize the ovum. Uterine contractility is very important for shedding the endometrium every month, for conception, maintenance of ongoing pregnancy, and gamete transfer. When uterine contractions are abnormal, symptoms of painful menstruation, endometriosis, and infertility are seen. Retrograde menstruation and the presence of endometriotic lesions are seen in the abdomen when the uterine contractibility is abnormal.[40] Another etiology seen in these patients is the dysfunction of hypothalamic-pituitary-ovarian axis which can lead to infertility due to the lengthened follicular phase and diminished peaked LH concentration, also known as luteal phase defect.

Pituitary dysfunction causes downregulation of the endometrial receptivity, poor oocyte quality, and thus disrupted synthesis of follicles.[37]

Treatment for Endometriosis-related Infertility

Evidence-based treatment for infertility associated with endometriosis includes the combination of medical and surgical treatment, after ruling out the other causes of infertility such as male factor, thyroid dysfunctions, hyperprolactinemia, and premature ovarian insufficiency.

In patients with endometriosis, staging is important to determine the treatment of infertility in such patients.

Endometriosis is staged from the stage (I-minimal, II-mild, III-moderate, and IV-severe) based upon the exact location, extent, and depth of the endometriotic implants, presence of the scar tissues, and presence of endometrial tissues in the ovaries.[41]

The *in vivo* intrauterine insemination with or without follicle stimulation is used in patients who have mild to moderate endometriosis. It involves the transfer of sperms high in the fundus of the uterine cavity. The sperm can be of partner or donor sperm, this treatment is mainly used for patients having mild endometriosis with patent tubes.

In vitro fertilization and embryo transfer (IVF-ET) is the treatment of choice in women who have compromised tubal function due to adhesions secondary to endometriosis, male factor infertility, and previous IVF treatment failures.

IVF is an *in vitro* process that involves the transfer of one or more embryos in the uterine cavity by externally fusing it in the laboratory.

For males, who have severely low-quality sperm with abnormal morphology, intracytoplasmic sperm injection is done. IVF ET is being encouraged for women having advanced endometriosis and it is considered as the first line of therapy.[40]

IVF-ET has produced a pregnancy rate of 56.1% in comparison to significant lower pregnancy of 37.4% with surgery alone.[42] However, the surgical procedure has been effective in removing the entire visible lesion during the laparoscopic intervention. Laparoscopic adhesiolysis has shown to improvise the fertility rate in patients with more severe stages of endometriosis.[36]

Future Perspective for Endometriosis-related Infertility

Future treatment is more targeted toward the molecular level, including use of immunotherapies to genes and tissue factors which are seen in endometriotic lesions. Low levels of Anti-Mullerian Hormone (AMH) are also seen in women who complain of infertility. It is used as a tool to access ovarian reserve.[43] It is notably reduced in women who have had ovarian surgeries. Therefore, women who desire fertility, AMH level can help in selecting in prioritizing and choosing patients for ovarian cystectomy as a fertility treatment.[44]

CONCLUSION

Endometriosis is a debilitating disease. Early diagnosis and management can halt the progression of this inflammatory disease and on the contrary, late diagnosis can lead to a decrease in reproductive ability and infertility.

Endometriosis impairs fertility in a multifactorial way, which adversely affects the ovarian reserve and child-bearing capacity depending on the stage and severity of the disease.

Early diagnosis and treatment are the key to this progressively and worsening disease. IVF is the best treatment of choice in patients who wish to conceive but have severe endometriosis which has impeded their normal child-bearing ability.

Medical treatment can only ameliorate the symptoms but shows no effect in increasing pregnancy rate. Treatment, therefore, must be individualized and taken into consideration as per the desire of the patient.

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AUTHORS' CONTRIBUTIONS

Jaanam Khan – Data collection, reviewing, and preparing the manuscript. Mutarba Khan, Arbaab Khan – editing the manuscript and reference management.

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Original Article

Refractive Errors among Medical Students – A Cross-sectional Study

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Abstract

Objective: The objective of the study was to determine the prevalence of refractive errors among the medical students of Nishtar Medical University Multan and to learn any impact of their daily routine on the incidence of the disease.

Materials and Methods: A cross-sectional study of 200 medical students of Nishtar Medical University (98 males and 102 females) was carried out. Forty students each from all five academic years of MBBS were selected using a simple random sampling technique. The chosen study population was explained the study's objectives and a written consent form was obtained from each student. The medical screening record of visual acuity was taken from the participants. Some additional ophthalmological examinations were also carried out by a senior consultant of the university's ophthalmological department to confirm the refractive error status. A questionnaire was also structured, containing information about their daily routines, habits, and personal information to assess some risk factors' possible association with refractive errors. The data were recorded on a data sheet for every individual, and the statistical analysis was performed using SPSS v.2.0 and Microsoft Excel.

Results: Out of 200 medical students, 119 (59.5%) had some or the other form of refractive error. The class-wise prevalence of refractive errors in successive years of MBBS from 1st to 5th year was 29 (72.5%), 21 (52.5%), 25 (62.5%), 25 (62.5%), and 19 (47.5%). Among those with refractive errors, 55 (46.2%) were male and 64 (53.7%) were female. In comparison, 109 (91.6%), 5 (4.2%), and 5 (4.2%) were myopes, hyperopes, and simple astigmatic, respectively. The applied tests of significance, that is, Chi-squared tests and Fischer's exact tests with a two-sided P value of <0.05%, were used. The studied variables in the study showed that gender, parental history of refractive errors, increased use of electronic gadgets, daily involvement in sports, frequent use of dietary supplements, use of appropriate light for studying, and regular practice of eye exercises were statistically significant in the prevalence of refractive errors among the medical students.

Conclusion: There is a high prevalence of refractive errors among Nishtar Medical University medical students, and myopia is the most prevalent refractive error. Several factors are studied in this study, which has a significant association with disease incidence.

Keywords: Astigmatism, Hypermetropia, Medical students, Myopia, Refractive errors

INTRODUCTION

Refractive error is defined as an error in focusing light on the retina, causing a decreased visual acuity.[1] The three most common types of refractive errors are as follows:

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- Myopia (Nearsightedness) – causing difficulty to focus far objects
- Hypermetropia (Farsightedness) – causing difficulty to focus near objects.

Astigmatism – this is distorted vision resulting from an irregularly curved cornea.[2]

Refractive errors are estimated to be the second most common cause of blindness worldwide in 2010[3] and one of the most familiar reasons for patients to visit an ophthalmologist. Academically active professionals, like medical students, are the primary sufferers of visual

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impedance.[4] It may be because they contact technology the most in their everyday activities, spend long hours reading and doing near work, not finding enough time for sports and physical activities, and acute academic stress to pass and compete.[5,6] Poor vision in students negatively influences their future life as it affects their productive performance in education and affects their professional competence and performance in the long-term.[7]

Unfortunately, there is a scarcity of studies addressing refractive error prevalence in Pakistan; however, a survey conducted on Singapore's medical students showed a prevalence rate of 82% for refractive errors.[8] Another study showed a prevalence of 54% for refractive errors among the medical students of India.[9] Therefore, medical students of Nishtar Medical University Multan were selected to determine the prevalence of various refractive errors and find an impact of their daily routine over the disease progression to get a record for this region.

MATERIALS AND METHODS

Study Design and Settings

It is a cross-sectional study conducted from March to May 2020 at Nishtar Medical University, Multan. Ethical issues were addressed according to the institutional review board.

The university has a medical screening policy for admitting students, where every student is screened for various medical illnesses, refractive error problems, and vaccination statuses. It has its medical board, including a highly specialized ophthalmologist that takes the best-corrected visual acuity using a Snellen chart, automated refractometer, doing some blood work, and followed by a medical interview. For our study, we took the medical screening record of visual acuity from the participating students. Some additional ophthalmological examinations were also carried out by a senior consultant of the university's ophthalmological department.

Among all 5 years of MBBS, 40 students from each class were selected, making 200 students, based on simple random sampling. The students of both sexes aged from 18 to 25 years. The chosen study population was explained the study's objectives, and a written consent form that stated the purpose, methods, risks, benefits, and the assurance of the confidentiality of the data was obtained from each student. The participation rate was 100%. The study was conducted over 2 months.

A questionnaire was structured to assess the possible association of some risk factors with refractive errors. It was adopted from different studies.[10,11] Some sections of the questionnaire were customized to fit the study population and the differences in the living environment that may impact quantifying outdoor and indoor activities. Previous studies have widely used the questionnaire-based method to quantify near-work and outdoor activities.[12,13] All questionnaires were filled by the study participants. The questions covered necessary information like demographic data, including name, age, gender, class, corrected refractive measurements, year of diagnosis, personal history of wearing spectacles or contact lenses, and parental refractive error status. The data regarding the average number of hours spent per day on near-work activities were collected from questions based on studying, using mobile phones, computer, and television. The data regarding the time spent on outdoor activities were collected from questions about involvement in sports and other outdoor hobbies. The participants were also asked about the use of any dietary supplement, appropriate light for studying, the practice of any eye exercise, eyewashes before going to bed, and also about their everyday nutritional habits.

Procedure and Data Analysis

The questionnaire-based data were collected, organized, summarized, analyzed, and later presented using Microsoft Excel and SPSS v.20. Chi-squared tests and Fisher's exact tests were used to test the association among categorical and continuous variables, respectively. For the analysis, a two-sided $P < 0.05$ was considered statistically significant.

RESULTS

The study comprises 200 medical students from the classes 1st to 5th year of MBBS, 40 students from each class with zero non-participation rate and ages ranged from 18 to 25 years. One hundred nineteen (59.5%) of 200 subjects had some or the other form of refractive error [Figure 1]; with 29 (72.5%), 21 (52.5%), 25 (62.5%), 25 (62.5%), and 19 (47.5%) students having refractive errors in successive years of MBBS from 1st to 5th year. Among those with refractive errors, 55 (46.2%) were male and 64 (53.7%) female [Figure 2]. In comparison, 109 (91.6%), 5 (4.2%), and 5 (4.2%) were myopes, hyperopes, and simple astigmatic, respectively. The overall mean age of respondents having refractive errors was 20.7 ± 1.65 years. On the contrary, 81 (40.5%) students had no refractive error [Figure 1].

The prevalence of refractive errors among different age groups of the studied population is shown in Table 1. The results show the maximum prevalence in the age group of 18–19 years.

The applied tests of significance showed that from the studied variables in the study such as gender, parental

Table 1: Prevalence of refractive errors in different age groups

Age groups	Students with refractive errors	Students without any refractive error	Total	Percentage of students with refractive errors
18–19	29	14	43	67.44
20–21	55	32	87	63.21
22–23	29	29	58	50
24–25	06	06	12	50

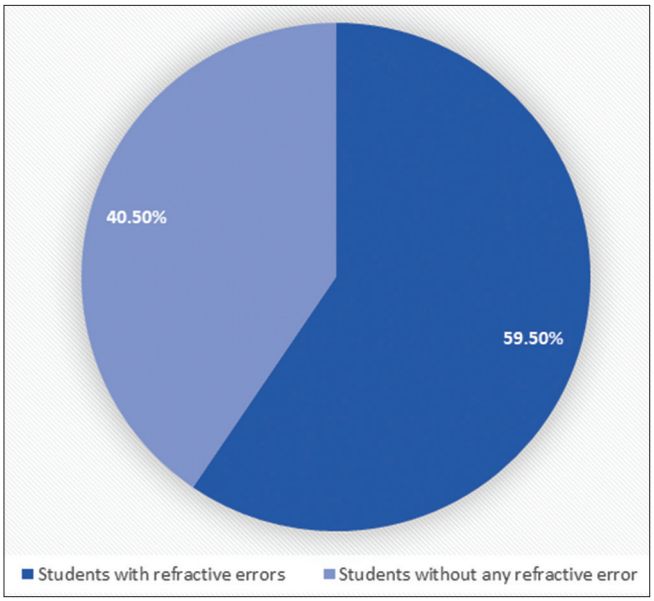

Figure 1: Total distribution of refractive errors among students

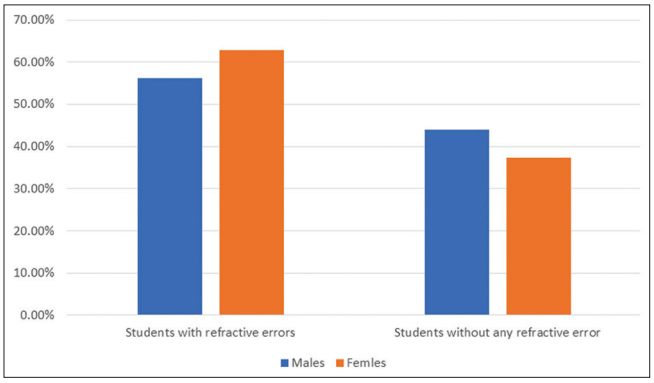

Figure 2: Gender-wise distribution of refractive errors among students

history of refractive errors, increased use of electronic gadgets, involvement in sports, frequent use of dietary supplements, use of appropriate light for studying, and regular practice of eye exercises, were statistically significant in the prevalence of refractive errors among the medical students [Table 2].

Gender-wise response to the questionnaire was recorded. After comparing the values of different variables between males and females having refractive errors, it was found that females have more prevalence of refractive errors than males and females have early diagnosis, more frequent change in prescription, more intense studying hours, fewer sports involvement, and more positive parental history and less habit of dietary supplement intake than males [Table 3].

Class-wise response to the questionnaire was also recorded. After comparing different variables, it was found that 1st-year students have more prevalence of refractive errors while other variables are found not to be comparable [Table 4].

DISCUSSION

This study has several important findings. Among the medical students aged from 18 to 25 years, the prevalence of refractive errors was 59.5%, following the results of similar studies conducted in India, showing a prevalence of 54% and 55%.[5,9] The majority of participants in our study were affected by myopia (91.6%) followed by hyperopia (4.2%) and astigmatism (4.2%). Such high prevalence of myopia in young medical students of Pakistan is supported by the studies on medical students of India (77.7%), Singapore (82%),[9] and Malaysia,[14] where myopia was also found to be higher as compared with other errors of refraction. However, such prevalence of myopia was quite high when compared to other countries. It was estimated to be 32.9%, 13%, 19.7%, and 34.2% in Turkish, Norwegian, Jordanian, and European students, respectively, aged 20–24.[15-18] The high reported prevalence of myopia observed in South-Asian students as compared to the East-Asian and Western students could be explained by the ethnic variations, different genetic predisposition and environmental factors; like the medical students of South-Asia spend less time outdoors as they are subjected to a more rigorous examination system.[13,19,20]

Regarding the prevalence among male and female participants, a significant difference was observed in this study. Similar results were seen in a survey of medical students of Saudi Arabia and Turkey.[16]

The presence of refractive parents' errors was a significant contributing factor in the prevalence of visual error defects in students under study, using

Table 2: Comparison of variables between students with refractive errors and students without any refractive error

Questions	Students having refractive errors *n*=119 (100%)	Students without any refractive error *n*=81 (100%)
Hours for studying		
Moderate	67 (56.30)	53 (65.43)
Intense	52 (43.70)	28 (34.57)
Hours for resting		
Moderate	46 (38.66)	37 (45.68)
Intense	73 (61.34)	44 (54.32)
Hours for using electronic gadgets		
Moderate	41 (34.45)	40 (49.38)
Intense	78 (65.55)	41 (50.62)
Involvement in sports		
Yes	21 (17.65)	36 (44.44)
No	98 (82.35)	45 (55.56)
Last professional grade		
Good	3 (2.52)	5 (6.17)
Average	116 (97.48)	76 (93.83)
Presence of refractive error in any parent		
Yes	90 (75.63)	40 (49.38)
No	29 (24.37)	41 (50.62)
Intake of dietary supplements		
Yes	24 (20.17)	28 (34.57)
No	95 (79.83)	53 (65.43)
Attitude toward review for visual assessment		
Every 6 months assessment	11 (9.24)	0 (0)
Every year assessment	20 (16.81)	4 (4.94)
When there are visual symptoms	88 (73.95)	77 (95.06)
Use of appropriate light for studying		
Yes	102 (85.71)	77 (95.06)
No	17 (14.29)	4 (4.94)
Practice of eye exercises		
Yes	6 (5.04)	19 (23.46)
No	113 (94.96)	62 (76.54)
Habit of eye wash at night		
Yes	39 (32.77)	34 (41.98)
No	80 (67.23)	47 (58.02)

Moderate: 1–4 h, Intense: More than 4 h, Good: Above 70%, Average: 60–70%

statistical significance tests. This result is also in agreement with similar studies done.[16,21] Parental refractive error status was sometimes interpreted as evidence for a genetic role; however, as there is growing evidence for the greater influence of environmental factors, it remains difficult to explain the complex interaction between environmental and genetic factors in the prevalence of refractive error. It is generally agreed now that both heredity and environment have important roles to play.[22,23]

The long and extensive study regimen of a medical school involves extensive near-work such as reading and writing.[8] Suggested that an increased amount of near-work could cause an early defective vision and its progression in adulthood.[22] The possible association between near-work activity and the prevalence of refractive error can be explained on the basis that increasing the amount of near-work done can consequently increase accommodation, which in turn could potentially cause defective vision, particularly myopia.[24] However, evidence from experimental animal studies has shown that accommodation is not an influencing factor.[25-28] Multiple studies have demonstrated an association of near-work with the prevalence of refractive errors. For instance, a longer axial length was substituted for myopia, and it showed association with a long time indoors.[29] Another study implied that for each additional 1 h of writing/reading or computer work, myopia's odds increased by 24% and 16%, respectively.[15] Our study also found a significant association between the prevalence of refractive errors and the amount of near-work performed. Since there is no universal definition for near-work, and hence quantification of near-work may vary, and so might the results. A questionnaire-based survey for quantifying near-work has been used in this study. However, it is prone to have recall bias in terms of recalling time spent on various near-work activities

Table 3: Gender-wise response to questionnaire by students having refractive errors

Questions	Male *n*=55(100%)	Female *n*=64 (100%)
Type of refraction error		
Myopia	52 (94.55)	57 (89.06)
Hypermetropia	1 (1.82)	4 (6.25)
Astigmatism	2 (3.64)	3 (4.69)
Time of diagnosis		
Before entering medical college	44 (80)	56 (87.50)
After entering medical college	11 (20)	8 (12.50)
No. of times the change in prescription after entering medical college		
None	24 (43.64)	34 (53.13)
Once	17 (30.91)	18 (28.13)
Twice	10 (18.18)	6 (9.38)
Thrice or more	4 (7.27)	6 (9.38)
Attitude toward the use of visual aids		
Class lectures only	9 (16.36)	28 (43.75)
Book reading only	4 (7.27)	2 (3.13)
Driving only	2 (3.64)	0 (0)
Using electronic gadgets only	0 (0)	4 (6.25)
Every time	40 (72.73)	30 (46.88)
Hours for studying		
Moderate	31 (56.36)	36 (56.25)
Intense	24 (43.64)	28 (43.75)
Hours for resting		
Moderate	21 (38.18)	25 (39.06)
Intense	34 (61.82)	39 (60.94)
Hours for using electronic gadgets		
Moderate	16 (29.09)	25 (39.06)
Intense	39 (70.91)	39 (60.94)
Involvement in sports		
Yes	18 (32.73)	3 (4.69)
No	37 (67.27)	61 (95.31)
Last professional grade		
Good	1 (1.82)	2 (3.13)
Average	54 (98.18)	62 (96.87)
Presence of refractive error in any parent		
Yes	39 (70.91)	51 (79.69)
No	16 (29.09)	13 (20.31)
Intake of dietary supplements		
Yes	12 (21.82)	12 (18.75)
No	43 (78.18)	52 (81.25)
Attitude toward review for visual assessment		
Every 6 months assessment	7 (12.73)	4 (6.25)
Every year assessment	12 (21.82)	8 (12.50)
When there are visual symptoms	36 (65.45)	52 (81.25)
Use of appropriate light for studying		
Yes	47 (85.45)	55 (85.94)
No	8 (14.55)	9 (14.06)
Practice of eye exercises		
Yes	1 (1.82)	5 (7.81)
No	54 (98.18)	59 (92.19)
Habit of eye wash at night		
Yes	15 (27.27)	24 (37.50)
No	40 (72.73)	40 (62.50)

Moderate: 1–4 h, Intense: More than 4 h, Good: Above 70%, Average: 60–70%

bedsides its possible inability to detect individual differences.

The protective role of daily outdoor sports from developing refractive errors has also been studied in various studies. Some did not find an association and some found only a weak association. Our study signifies that students involved in daily sports activities and spent less time indoors had a low prevalence of refractive error. A similar association was reported in other studies too.[11,12,15]

It was also found that the students who regularly took dietary supplements, studied under appropriate light, and practiced regular eye exercises had less chance of developing refractive errors. However, this association is not supported by adequate evidence from studies.

Table 4: Class-wise response to questionnaire

Questions	Class (1st year) *n*=40 (100%)	Class (2nd year) *n*=40 (100%)	Class (3rd year) *n*=40 (100%)	Class (4th year) *n*=40 (100%)	Class (5th year) *n*=40 (100%)
Type of refraction error					
Myopia	28 (70)	18 (45)	22 (55)	24 (60)	17 (42.5)
Hypermetropia	1 (2.5)	2 (5)	1 (2.5)	1 (2.5)	0 (0)
Astigmatism	0 (0)	1 (2.5)	2 (5)	0 (0)	2 (5)
Time of diagnosis					
Before entering medical college	26 (65)	19 (47.5)	20 (50)	21 (52.5)	14 (35)
After entering medical college	3 (7.5))	2 (5)	5 (12.5)	4 (10)	5 (12.5)
No. of times the change in prescription after entering medical college					
None	23 (57.5)	5 (12.5)	13 (32.5)	10 (25)	7 (17.5)
Once	1 (2.5)	12 (30)	5 (12.5)	10 (25)	7 (17.5)
Twice	5 (12.5)	3 (7.5)	2 (5)	3 (7.5)	3 (7.5)
Thrice or more	0 (0)	1 (2.5)	5 (12.5)	2 (5)	2 (5)
Attitude toward the use of visual aids					
Class lectures only	9 (22.5)	6 (15)	8 (20)	9 (22.5)	5 (12.5)
Book reading only	2 (5)	1 (2.5)	0 (0)	1 (2.5)	2 (5)
Driving only	1 (2.5)	0 (0)	0 (0)	1 (2.5)	0 (0)
Using electronic gadgets only	0 (0)	1 (2.5)	3 (7.5)	0 (0)	0 (0)
Every time	17 (42.5)	13 (32.5)	14 (35)	14 (35)	12 (30)
Hours for studying					
Moderate	17 (42.5)	10 (25)	13 (32.5)	15 (37.5)	12 (30)
Intense	12 (30)	11 (27.5)	12 (30)	10 (25)	7 (17.5)
Hours for resting					
Moderate	10 (25)	8 (20)	9 (22.5)	13 (32.5)	6 (15)
Intense	19 (47.5)	13 (32.5)	16 (40)	12 (30)	13 (32.5)
Hours for using electronic gadgets					
Moderate	10 (25)	6 (15)	9 (22.5)	9 (22.5)	7 (17.5)
Intense	19 (47.5)	15 (37.5)	16 (40)	16 (40)	12 (30)
Involvement in sports					
Yes	6 (15)	1 (2.5)	3 (7.5)	7 (17.5)	4 (10)
No	23 (57.5)	20 (50)	22 (55)	18 (45)	15 (37.5)
Last professional grade					
Good	2 (5)	1 (2.5)	0 (0)	0 (0)	0 (0)
Average	27 (67.5)	20 (50)	25 (62.5)	25 (62.5)	19 (47.5)
Presence of refractive error in any parent					
Yes	17 (42.5)	18 (45)	18 (45)	21 (52.5)	16 (40)
No	12 (30)	3 (7.5)	7 (17.5)	4 (10)	3 (7.5)
Intake of dietary supplements					
Yes	7 (17.5)	3 (7.5)	0 (0)	6 (15)	8 (20)
No	22 (55)	18 (45)	25 (62.5)	19 (47.5)	11 (27.5)
Attitude toward a review for visual assessment					
Every 6 months assessment	2 (5)	2 (5)	2 (5)	3 (7.5)	2 (5)
Every year assessment	3 (7.5)	1 (2.5)	4 (10)	4 (10)	8 (20)
When there are visual symptoms	24 (60)	18 (45)	19 (47.5)	18 (45)	9 (22.5)
Use of appropriate light for studying					
Yes	24 (60)	20 (50)	20 (50)	23 (57.5)	15 (37.5)
No	5 (12.5)	1 (2.5)	5 (12.5)	2 (5)	4 (10)
Practice of eye exercises					
Yes	1 (2.5)	0 (0)	0 (0)	4 (10)	1 (2.5)
No	28 (70)	21 (52.5)	25 (62.5)	21 (52.5)	18 (45)
Habit of eye wash at night					
Yes	11 (27.5)	6 (15)	4 (10)	11 (27.5)	7 (17.5)
No	18 (45)	15 (37.5)	21 (52.5)	14 (35)	12 (30)

Moderate: 1–4 h, Intense: More than 4 h, Good: Above 70%, Average: 60–70%

CONCLUSION

It is concluded that there is a high prevalence of refractive errors among the medical students of Nishtar Medical University Multan, and myopia is found to be the most prevalent refractive error. Several factors such as parental history of refractive errors, increased use of electronic gadgets, involvement in daily sports, frequent use of dietary supplements, use of appropriate light for studying, and regular practice of eye exercises, which have a significant association with the disease incidence.

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Original Article

A Prospective Study Comparing Prevalence of Different Antiphospholipid Antibodies in Pregnant Women with Recurrent Pregnancy Loss

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Abstract

Introduction: Prospective study comparing prevalence of different antiphospholipid antibodies (APAs) in pregnant women with recurrent pregnancy loss.

Materials and Methods: The patients recruited in the study would include those attending the OBG outpatient department at kurji Holy Family Hospital, Patna. After thorough history and clinical examination, routine blood investigations were sent. Patients were counseled about benefits of APLA test and its implications in pregnancy outcome. Consent was taken and patients were informed that if test is positive than she would have to undergo repeat test 12 weeks later for confirmation of diagnosis. Patients blood were collected into two separate bulbs one in plane bulb (2 ml blood) by which b2GP1 and ACL antibodies were detected by ELISA and other is citrate bulb (containing 0.2 ml of trisodium citrate 3.2%+1.8 ml of freshly collected blood) which detect LA.

Results: Among 120 patients, 23 patients (19.1%) were positive for APLA antibodies among which 11 cases were (9.16%) positive for lupus anticoagulant, 6 cases were anticardiolipin antibodies. Out of 6 cases, 2 (1.6%) cases positive for anticardiolipin antibodies IgG and 4 (3.33%) were positive for IgM. The positivity of anti-beta-2 glycoprotein 1 in our study was 5% in which 4 cases (3.33%) positive for IgG and 2 (1.6%) cases were positive for IgM antibodies. Among 23 patients of APLA positive, 16 were started on LMWH and 14 patients of APLA negative were also started on LMWH the outcome was not statistically significant. Among APLA positive out of 23, 12 cases delivered by LSCS, 7 by PTVD, 3 by FTVD, and 1 case missed and the indication of LSCS as was fetal distress in 4 women, severe oligohydramnios in 3 cases, 2 for severe preeclampsia, 2 for abruption, and 1 for failed induction. We also followed up the babies of these patients. Ninety-three babies were healthy and given to mother in which 14 babies were of APLA-positive mother, 20 neonates were admitted to NICU for prematurity or fetal distress out of which 6 patients of APLA-positive women, 3 had IUD 2 of which APLA positive, 3 neonatal death in which 1 neonate of APLA-positive women. We also note the complications among women in which preeclampsia was present in seven patients out which six were APLA positive. Among APLA positive, six patients had IUGR, five patients had abruption, one had vascular complications, and seven had severe oligohydramnios. Antithrombotic interventions are essential to have a favorable outcome in high-risk pregnancies in association with APLA antibodies and thus the need of these high-risk pregnancies for APLA.

Conclusion: The association of APLA antibodies in high-risk pregnancy with a history of recurrent miscarriages was found to be 19.1% in the present study. The incidence of APLA antibodies in general population is 5–20%, it is proved fact that the APAs interfere with normal development of the uteroplacental circulation to cause both early and late pregnancy loss. Based on the concept of APAs induced thrombophilia and placental thrombosis, antithrombotic interventions have been widely applied to reduce the incidence of miscarriages and fetal loss. The outcome of high-risk pregnancies in APLA syndrome is considerably improved by initiation of therapies using aspirin, unfractionated heparin, and/or low-molecular-weight heparin. The antiphospholipids have been the most important cause for recurrent fetal loss, thus, many pregnancies can be saved if diagnosis and treated adequately. This can be done by routine screening for the antiphospholipids antibodies in pregnant women with a bad obstetric history and unexplained fetal loss. Close antenatal surveillance and planned delivery of these pregnancies in a unit with specialist obstetrics and neonatal intensive care facilities are indicated.

Key words: ACA(anticardiolipin antibody), Antibeta2GLP1, APLA (antiphospholipid antibody), RPL (recurrent pregnancy loss)

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INTRODUCTION

Recurrent pregnancy loss (RPL) is a common problem in obstetrics. It affects about 5–15% of all pregnancies worldwide.[1] It affects between 1 in 300 and 1 in 100 couples worldwide.[2] RPL is encountered in 5% of couples with two or more losses and in around 1–2% of couples with three or more losses.[3]

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The Royal College of Obstetricians and Gynecologists and the European Society of Human Reproduction and Embryology define recurrent miscarriage as three or more consecutive losses before 24 weeks gestation[4] Due to an increasing number of childless couples, the improved availability of diagnostic tests, and most importantly the minimal difference in the prognostic value between two and three losses, the American Society for Reproductive Medicine updated the definition of RPL to two or more clinical pregnancy losses, before 20 weeks period of gestation, documented by either ultrasonography or approved in a histopathologic examination.[4]

A large number of etiological factors are associated with RPL, in approximately two-third of cases, the cause is known to be genetic error, anatomic abnormalities of the reproductive tract, hormonal abnormalities, infection or immunologic factors, or systemic disease, whereas, idiopathic in one-third of all cases.[5]

There is a great deal of interest in the role inherited thrombophilia in RPL. Thrombophilias can be hereditary thrombophilias (HTs) or acquired thrombophilias (ATs). The most common HT is due to Factor V Leiden, prothrombin gene mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency accounting for other causes.[6] ATs are mostly attributed to antiphospholipid syndrome (APS) which is encountered in 5–20% of patients with RPL.

Antiphospholipid antibodies (APAs) are group of antibodies that bind to negatively charged phospholipids. APAs are heterogeneous group of autoantibodies directed against different antigens, predominantly anionic phospholipids, or phospholipids containing structures.[7] APAs that associated with APS are anticardiolipin antibodies (ACAs) or antibodies against other negatively charged phospholipids such as phosphatidylserine, phosphatidylinositol, phosphatidic acid, and phosphatidylglycerol.[8] Lupus anticoagulants (LAs) which are immunoglobulins directed against plasma proteins such as prothrombin or annexin V that are bound to phospholipids. Anti-b_2 glycoprotein 1 is antibodies which recognize a plasma protein known as apolipoprotein H or beta-2 glycoprotein I and has higher specificity than ACA for thrombosis.[9]

The presence of the APAs was shown to associate with recurrent miscarriage due to thrombosis of the uteroplacental vasculature and subsequent placental infarct.

There is an increasing burden of RPL in the society and APS being one of the undisputed treatable causes for RPL. This study aims to evaluate the significance of the antibody profiles of APS in relation to RPL.

MATERIALS AND METHODS

Study Design

The patients recruited in the study were included those attending the OBG outpatient department at kurji Holy Family Hospital, Patna.

Study Population

Inclusion criteria

History of two or more previous spontaneous pregnancy losses with

- Ultrasound confirmed pregnancy with intrauterine gestation sac
- Less than 20 weeks of gestation
- With or without fetal cardiac activity.

Exclusion criteria

The following criteria were excluded from the study:

- Previous medical termination of pregnancy
- Previous ectopic pregnancy
- Previous pregnancy losses of more than 20 weeks gestation
- Trauma-induced previous pregnancy loss.

Data Collection

After thorough history and clinical examination, routine blood investigations were send. Patients were counseled about benefits of APLA test and its implications in pregnancy outcome. Consent was taken and patients were informed that if test is positive then she would have to undergo repeat test 12 weeks later for confirmation of diagnosis. Patients blood were collected into two separate bulbs one in plane bulb (2 ml blood) by which b2GP1 and ACL antibodies were detected by ELISA and other is citrate bulb (containing 0.2 ml of trisodium citrate 3.2% + 1.8 ml of freshly collected blood) which detect LA.

Sample Size

About 4000 cases come in OPD per year, out of which about 60–70 patients are of RPL. Now using Raosoft formula with 95% confidence level and 5% margin of error, sample comes out to be 60.

$$Y=z(c/100)^2r\ (100-r)$$
$$n=Ny/(N-1)E^2+y$$
$$E=sqrt[(N-n)y/n(N-1)]$$

For 2 years of study, my sample was about 120.

Study Duration

This study was from November 2017 to October 2019.

Methodology

Written and informed consent was taken from all the patients after brief explanation of the procedure. Ethical

clearance was obtained from Institute's Ethical Clearance Committee.

A detailed history of patients will be take based on set questionnaires about pregnancy loss like weeks at which abortion occurs, was pregnancy confirmed or not any history of curettage, hypertension, DM, thyroid disorders, etc. Detailed general and gynecological examination findings were taken. Routine blood investigations were sent along with investigations for APLAs which included LA, anticardiolipin antibody (ACA), and anti-β2 glycoprotein 1 (Anti-β2GP1Ab). If any of the above-mentioned tests for APAs will come positive for a patient, a repeat of that particular test will be done after 12 weeks, since the diagnosis of APS requires a test to be positive on two or more occasions at least 12 weeks apart. LA will be measured using dilute Russell viper venom test using the principle of electromechanical clot detection. Normal values are between 32 and 42 s with higher values suggestive of antibody positivity. Serum ACA levels were tested by enzyme immune assay method. Values >15GPL for IgG antibody subtype and >12.5 MPL for IgM antibody subtype will be taken as positive. Serum anti-β2GP1Ab levels will be tested by enzyme immune assay method. Values >20 SGU for IgG type and >20 SMU for IgM type antibody will be considered to be positive. Statistical analyses will be done using SPSS version 18. Prevalence data will be noted as percentages or proportions. Categorical variables were compared using Fisher's exact test while continuous variables were compared using Student's t-test. $P < 0.05$ was taken to be statistically significant. Consent was taken from all the participants on consent forms written in the language comfortable to them.

RESULTS

Table 1 shows that among 120 cases, 23 were found to be APLA positive and 97 were APLA negative (19.2%). Figure 1a and b shows the total 23 cases of APLA positive in which 13 cases were below 25 years age group and 10 cases were above 25 years age group.

Table 2 shows that APLA was positive in 25 cases when tested 1st time when these positive results subjected for APLA test repeat after 12 weeks ,2 samples were negative (8.6%). Hence, in our study, 23 out of 120 cases were APLA positive (19.6%).

Table 3 shows the positive APLA antibodies detected in the study. The positive samples were repeated 12 weeks later. There were two samples of ACL IgG positive, four samples of ACL IgM positive, four of beta 2-glycoprotein 1 IgG positive, and four of beta 2-glycoprotein 1 IgM in which 2 samples were positive and 11 samples positive for LA.

Table 4 shows among APLA positive two cases of ACL IgG positive were less than 25 years of age, one case of ACL IgM positive was less than 25 years, and three were more than 25 years, one case of anti-B2 glycoprotein IgG positive was less than 25 years, and three were more than 25 years, three cases of anti-B2 glycoprotein IgG positive were less than 25 years, and one case of anti-B2 glycoprotein IgG positive was more than 25 years, among 11 cases of LA positive, seven cases were less than 25 years and four cases were more than 25 years.

Table 5 shows among APLA-positive women, 20 cases (86.95%) had primary RPL and 3 cases (13%) had secondary RPL.

Table 1: Age distribution APLA positive and negative

AGE	APLA +VE	APLA -VE	TOTAL	P VALUE
<25	13(25.5%)	39(75%)	52	.156
>25	10(14.2%)	58(85.3%)	68	
TOTAL	23(19.2%)	97(80%)	120(100%)	

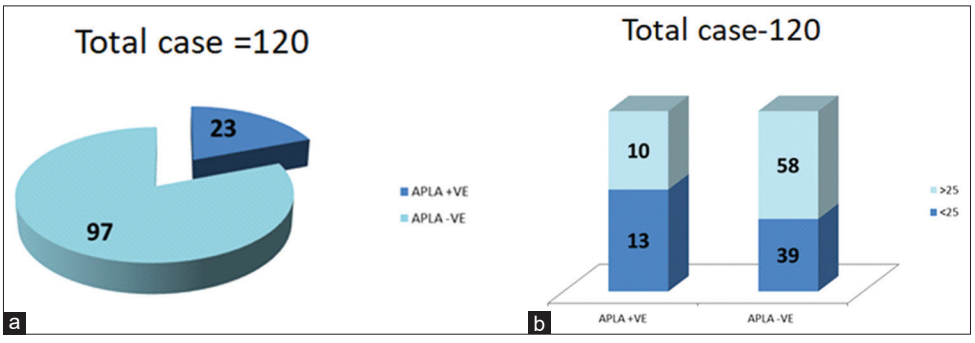

Figure 1: (a) Pie chart showing distribution of APLA positive and negative in the study. (b) Bar graph showing age distribution of APLA

Table 6 shows among 23 patients of APLA positive, 17 were started on LMWH which is statistically significant, and among APLA-negative patients, 13 patients were started on LMWH.

Table 6 shows among all patients 3 patients undergone FTVD (6.9%), 11 cases undergone LSCS (20.3%), 7 cases undergone PTVD (46.6%) which are APLA positive, and we lost follow-up of 8 cases either due to migration and non-communication.

Table 7 shows among 23 cases of APLA positive, 15 were (65.21%) undergone preterm delivery and 7 were undergone term delivery either by LSCS or NVD and 1 case had lost due to either delivery outside or irregularly follow-up.

Table 2: Baseline APLA positive and repeat test after 12 weeks

APLA	BASELINE	APLA +VE	APLA –VE
NEGATIVE	95	0	95(100%)
POSITIVE	25	23(92%)	2(8.6%)
TOTAL	120	19.1%	80.8%

Table 3: Distribution of individual APLA antibodies at baseline and repeat after 12 weeks

APLA ANTIBODIES	POSITIVE RESULTS	REPEAT AT 12 WEEKS (NEGATIVE RESULT)	TOTAL
ACLIgG	2	0	2(100%)
ACLIgM	4	0	4(100%)
B2GP1IgG	4	0	4(100%)
B2GP1TgM	4	2	2(50%)
LA	11	0	11(100%)
TOTAL	25	2	23(92%)

Table 9 shows among APLA positive, 6 had preeclampsia, most of the patient 12 had IUGR, 2 patients had unexplained IUD, 5 patients had abruption, 1 had vascular complications, and 7 patients had oligohydramnios.

Table 10 shows among APLA positive patients, 6 neonates admitted in NICU, 2 patients had unexplained IUD, 1 neonate died, and 14 patients neonates were healthy.

DISCUSSION

The study was conducted in 120 patients presented to kurji Holy Family Hospital, Patna, either outpatient department or inpatient in the Department of Obstetrics and Gynaecology.

The overall positivity of APLA syndrome in RPL patients in our institute is 19.2% which is significantly less compared to the study which was conducted in 2018 Akansha Sharma *et al.*[10] from SDMH Jaipur, where 130 patients were taken with BOH in non-pregnant state. They found that overall APLA positivity was 27.69%. There were 13 (25.5%) APLA-positive cases below the age of 25 years and 10 (14.2%) cases above 25 years. Another study by Ravindram *et al.*[11] in 2016 found that overall positivity of APLA in women with adverse pregnancy outcome was 12.5% which was lower than our study.

The study was conducted in 120 patients having RPL. Out of 120 patients, 23 cases were found to be APLA positive which included anticardiolipin IgG/IgM, anti-beta-2 glycoprotein-1 IgG/IgM, and LA. When these positive samples repeated after 12 weeks according to Sapporo APS criteria 2006, two were APLA negative. The repeat test after 12 weeks showed two negative cases of anti-beta-2 GP1 IgM.

Table 4: Age distribution of individual APLA antibodies

Markers	Result	Age (%)		Total (%)	*P*-value
		<25	>25		
Anticardiolipin IgG	+VE	2 (100)	0	2 (100)	
	–VE	50 (42.4)	68 (57.6)	118 (100)	
Total		52 (43.3)	68 (56.7)	120 (100)	
Anticardiolipin IgM	+VE	1 (25)	3 (75)	4 (100)	
	–VE	52 (44)	65 (56)	116 (100)	
Total		52 (43.3)	68 (56.7)	120 (100)	
Anti-B2 glycoprotein IgG	+VE	1 (25)	3 (75)	4 (100)	
	–VE	51 (44)	65 (56)	116 (100)	
Total		52 (43.3)	68 (56.7)	120 (100)	
Anti-B2 glycoprotein IgM	+VE	2 (100)	0	2 (100)	
	–VE	49 (42.2)	67 (57.8)	116 (100)	
Total		52 (43.3)	68 (56.7)	120 (100)	
Lupus	+VE	7 (63.6)	4 (36.4)	11 (100)	Fisher's exact test *P*-value=0.154
	–VE	45 (42.3)	64 (58.7)	109 (100)	
Total		52 (43.3)	68 (56.7)	120 (100)	

Table 5: Distribution of primary RPL and secondary RPL among APLA-positive and -negative samples

APLA	PRI RPL (%)	SEC RPL (%)	Total (%)	*P*-value
–VE	78 (80.4)	19 (19.58)	97 (100)	Fisher's exact=0.000
+VE	20 (86.95)	3 (13)	23 (100)	
	98 (81.66)	22 (95.65)	120 (100)	

Table 6A: The patient started on LMWH, mode of delivery

LMWH	Result	APLA (%)		Total	*P*-value
		Negative	Positive		
LMWH	No	83 (92.2)	7 (7.7)	90 (100)	0.000
	Yes	14 (46.6)	16 (53.3)	30 (100)	
		97 (80.8)	23 (19.1)	120 (100)	

Table 6B: The patient started on LMWH, mode of delivery

MOD	APLA –VE (%)	APLA +VE (%)	Total (%)
FTND	40 (93.5)	3 (6.9)	43 (100)
LSCS	42 (77.7)	12 (22.2)	54 (100)
PTVD	8 (53.3)	7 (46.6)	15 (100)
NO	7 (87.5)	1 (12.5)	8 (100)
Total	97 (80.8)	23 (19.1)	120 (100)

In the current study, the overall 6 cases (5%) were of ACAs positive associated in women with RPL. Out of 6 cases, 2 (1.6%) cases positive for ACA IgG and 4 (3.33%) were positive for IgM. These antibodies cause pregnancy loss by defective implantation and subsequently defective placentation. In study of Sharma *et al.*, the overall positivity of ACAs is 18.46% in 130 patients with BOH where ACA IgG was 13.8%, ACA IgM was 10%, and both were 5.38% which is more than our study. Another study conducted by Dhason *et al.*[12] in 2016 in MMC Tamil Nadu in 100 pregnant women with BOH and 110 healthy pregnant women found that the overall positivity of ACAs was 21% of women with BOH and 7.6% in women without BOH.

The positivity of anti-beta-2 glycoprotein 1 in our study was 5% in which 4 cases (3.33%) positive for IgG and 2 (1.6%) cases were positive for IgM which is less than compared to the study of Sharma *et al.*[10] in which positivity of anti-beta-2 GLP1 is 6.92%.

The positivity of LA in our study was 9.16% which is more as compared to the study conducted by Sheela *et al.*[13] in 2016 in Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, in 56 women with RPL found that the overall positivity of LA was 6.06%. It is a pro-thrombotic agent and is thought to interact with platelets membrane

Table 7: Distribution of time of delivery among APLA positive and negative

APLA	<37 weeks (%)	>37 weeks (%)	No (%)	Total (%)
Negative	19 (19.58)	71 (73.19)	7 (7.21)	97 (100)
Positive	15 (65.21)	7 (30.43)	1 (4.3)	23 (100)

Table 8: Distribution of indication of LSCS among APLA positive and negative

INDICATION	APLA +VE	APLA –VE	TOTAL
FOETAL DISTRESS	12	4	16
ABRUPTIO PLACENTA	4	2	6
BREECH	8	0	8
FAILED I0L	9	1	10
SEVERE PRECLEMPSIA	1	2	3
SEVERE OILIGOHYDROMINOS	3	3	6
CORD PROLAPSE	1	0	1
DTA	1	0	1
PREVIOUS LSCS	4	0	4
TOTAL	43	12	55

Table 9: Distribution of complications among APLA positive and negative

Complications	APLA negative	APLA positive	Total
Preeclampsia	1	6	7
IUGR	24	12	36
IUD	1	2	3
Abruption	12	5	17
Vascular complications	1	1	2
Oligohydramnios	9	7	16

Table 10: Distribution of neonatal outcome among APLA positive and negative

NEONATAL COMPLICATION	APLA +VE	APLA -VE	TOTAL
NICU ADDMISSION	6(30%)	14(70%)	20(100%)
IUD	2(66.7%)	1(33.3%)	3(100%)
DEATH	1(33.3%)	2(66.7%)	3(100%)
NO COMPLICATION	14(15.1%)	79(84.9%)	93(100%)
TOTAL	23(18.9%)	97(79.5%)	120(100%)

phospholipids, thus increasing adhesion and aggregation of platelets, which results in pro-thrombotic characteristics,[14] and these antibodies are studied to cause thrombosis in the maternal circulation.

Among APLA-positive women, 86.95% had primary RPL and 13% had secondary RPL which was more when compared to the study of Sharma *et al.*[10] in which 83.33% of women had primary RPL.

In our study, the mode of conception among APLA-positive women was spontaneous in 91.30% and by ART in 8.6% which was more than the study by Sharma *et al.*[10]

in which spontaneous conception occurred in 83.33% of women and by ART in 16.67% of women.

As the etiology of placental thrombosis was thought to be cause of pregnancy loss in APLA syndrome, many studies were conducted and found that the heparin prevents the fetal loss by its anticomplement activation and thus places complement activation and inflammation at the level of pathogenic line, with thrombosis being a downstream terminal event. In our study among APLA positive out of 23 cases, 16 (53.3%) were on LMWH and 7 cases were not on LMWH either due poor compliance or non-affordability, and among APLA-negative women, 14 (46.6%) cases were on LMWH and they were follow up. Among APLA positive, 15 cases were regularly follow-up with us and 8 were lost their follow-up either due to migration or lack of concern for further evaluation but we maintained our follow-up by telephone.

Mode of delivery among APLA- positive women in our study out of 23, 12 cases delivered by LSCS, 7 by PTVD, 3 by FTVD, and 1 case missed. Table 8 shows among APLA positive women, indication of LSCS was fetal distress in 4 women, oligohydramnios in 3 cases, 2 for severe preeclampsia, 2 for abruption, and 1 for failed induction.

In our study, the time of delivery among 23 cases of APLA-positive women, 15 (65.21%) delivered preterm either by LSCS or PTVD out of 23 APLA positive, 12 cases were on LMWH and 7 (30.43%) out of which 4 on LMWH cases were delivered at term in APLA-negative women, out of 97 women, 19 (19.55%) were delivered preterm and 71 (73.19%) women delivered at term in which three cases and 10 cases were on LMWH, respectively. Most common cause of PTVD in our study was either spontaneous onset or induction of labor due to any fetal or maternal indication. Another study of Rai *et al*.[15] concluded in their study that treatment with aspirin and LMWH resulted in significantly higher rates of live births in APLA-positive women with a history of recurrent miscarriages.

APL antibodies complicate pregnancy by antibodies directed against cell membrane PLs which result in a hypercoagulable state that causes thrombosis and obstetrics complications. These antibodies react with endothelial structure that disturbs the balance of prostaglandin E2/thromboxane production resulting in early-onset preeclampsia and associated complications. Our study group was the 120 women who had unexplained RPL out of which 23 cases were APLA positive we follow the patients of both groups and found that among 6 (26.08%) cases had preeclampsia out of which 3 positive for LA, 2 for ACA IgM, and 1 for anti-beta-2 GLP1 IgG, 12 (52.17%) which was compared to the study of Dadhwal *et al*.[16] in 2011 in AIIMS, Delhi, found that among APLA-positive women who was on treatment (30.9%) had preeclampsia which similar to our study. Twelve (52.17%) cases had IUGR baby out of which 7, 2, 1, 1, and 1 cases positive for LA, anti-beta-2 GLP1 IgM, anti-beta-2 GLP1 IgG, ACA IgM, and ACA IgG. Two (8.6) cases had IUD both were positive for LA and both were not on LMWH which suggest that LMWH has the protective role in live birth in APLA-positive cases. Five cases had abruption in which three were positive for LA and two positive for anti-beta-2 GLP1 IgG. Five (21.7%) cases were complicated by Abruptio out of which three were positive for LA and two for anti-beta-2 GLP1 IgG and out five, three were on LMWH which was compared to the study conducted by Dadhwal *et al*.[16] in which out of 42 patients of APLA positive, 9 (21.4%) had IUGR which was less than our study, 2 (4.7%) were IUD which was on treatment as compared to IUD of our study both were had no treatment and 3 (7.1%) women had abruption which was significantly less as compare our study. Seven (30.4%) cases were having oligohydramnios.

The clinical manifestations of APLA include vascular thrombosis and pregnancy complications as described in Sapporo APS classification 20 criteria 2006, especially recurrent miscarriages and less frequently maternal thrombosis. In our study, two patients had RPL out of which 1 (4.3%) was APLA positive and it was positive for ACA IgM. This shows that IgM antibodies are associated with major complications as compare to IgG.

We also analyzed neonatal outcome in our study in which out of 120 cases, 14 (15.1%) cases of APLA positive and 79 (84.9%) cases of APLA negative had no complications. Twenty-three neonates were admitted to NICU either due to prematurity or respiratory distress in which 6 (26%) were APLA positive and 16 (69.5%) were negative for APLA there were 3 cases of IUD in which 2 cases (66.6%) were APLA positive. The cause of IUD was explained by fetal hypoxia due to reduced placental perfusion, hypertensive disorder, and abruption. There were three early neonatal deaths in which 1 (33.3%) was APLA positive. The neonatal death due to prematurity or sepsis. A similar study was conducted by Helgadotir *et al*.[17] which showed that the IUD associated with antiphospholipid antibodies. A case–control study was done on 105 healthy women with a history of IUD after 22 weeks of gestation and 262 controls with live births. Thus, concluding the women with a history of IUD after 22 weeks was most often associated with LA positive similar to our study in which both IUDs were LA positive. Gonen *et al*.[18] studied the prevalence on women with APS and unexplained IUD as compared to controls after 26 weeks of gestation and found that the LA and ACA antibodies were significantly more prevalent in women with IUD. The cause

of fetal IUD in APLA syndrome is initiation of activation of endothelial cells, monocytes, and platelets, causing an overproduction of tissue factor and thromboxane A2. This complement activation might have a central role. These factors result in typical changes in the hemostatic system during normal pregnancy, results in the hypercoagulable state leading to thrombosis that is presumed to provoke may of the pregnancy complications associated with APS including intrauterine fetal death of the fetus.

CONCLUSION

The association of APLA antibodies in high-risk pregnancy with a history of recurrent miscarriages was found to be 19.1% in the present study. The incidence of APLA antibodies in general population is 5–20%, it is proved fact that the APAs interfere with normal development of the uteroplacental circulation to cause both early and late pregnancy losses. Based on the concept of APAs induced thrombophilia and placental thrombosis, antithrombotic interventions have been widely applied to reduce the incidence of miscarriages and fetal loss. The outcome of high-risk pregnancies in APLA syndrome is considerably improved by initiation of therapies using aspirin, unfractionated heparin, and/or low-molecular-weight heparin. The antiphospholipids have been the most important cause for recurrent fetal loss, thus, many pregnancies can be saved if diagnosis and treated adequately. This can be done by routine screening for the antiphospholipid antibodies in pregnant women with a bad obstetric history and unexplained fetal loss. Close antenatal surveillance and planned delivery of these pregnancies in a unit with specialist obstetrics and neonatal intensive care facilities are indicated.

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Original Article

Current Scenario of Leprosy from a Referral Hospital, Tamil Nadu

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Abstract

Background: Leprosy, a chronic infectious disease, is a major public health concern in India. Thus, acquiring knowledge of its epidemiological variations is essential so that strategies for case detection and disease control can be made.

Aim: The objective of this study is to estimate the current scenario of leprosy from a referral hospital, Tamil Nadu.

Materials and Methods: Patients who attended dermatology department with signs and symptoms of leprosy from January 2016 to December 2019 were included in the study and their epidemiological and clinical profiles were recorded.

Results: A total of 212 patients were enrolled. Male/female ratio was 2.5:1. Majority of cases were between 41 and 60 years. Borderline tuberculoid was the most common type. Around 56% of patients had multibacillary (MB) leprosy. Lepra reactions were seen in 21.2% of cases and deformities were noticed in 15% of cases. Ulnar claw hand was the common deformity noted.

Conclusion: The number of new patients, MB proportion, and deformity among new patients were not in decreasing trend as expected in this post-elimination era. This highlights the urgent need for community-based appropriate strategy to break the chain in transmission of leprosy.

Key words: Deformity, Elimination, Leprosy, Multibacillary, Multidrug therapy, Reactions, World Health Organization

INTRODUCTION

Leprosy is one of the chronic infectious diseases that affect skin and peripheral nerves. *Mycobacterium leprae*, the causative organism, is transmitted by droplet spread which is facilitated by close contact.

Despite the prevalence rate being <1 case per 10,000 population, India still contributes more than 50% of new cases detected globally every year.[1] To understand the current trend of leprosy in post-elimination era, this study was conducted.

MATERIALS AND METHODS

This descriptive study was conducted in the Dermatology Department, Govt. Theni Medical College Hospital, Theni, Tamil Nadu, from January 2016 to December 2019.

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All patients who fulfilled the case definition of leprosy (one of the three cardinal features of leprosy) were included in the study. Age, sex, clinical spectrum of the disease, paucibacillary (PB) or multibacillary (MB), presence of lepra reaction, and disabilities were noted.

Clinical spectrum of the patient was decided after careful clinical examination, if needed also by slit skin smear examination and skin biopsy. The cases were divided into PB/MB according to the WHO criteria. (Number of skin lesions 1–5, with no nerve or only one nerve involvement with negative slit skin smear at all sites, was considered as PB, while number of skin lesions 6 and above with more than 1 nerve involvement with positive slit skin smear at any site was considered as MB).

Type I lepra reaction was diagnosed if the patient had redness, swelling (or) tenderness over the lesions, presence of edema of hands and feet or face, or tenderness of one or more nerves with or without nerve function impairment.

Type II lepra reaction was diagnosed if the patient had multiple, small, tender, evanescent nodules, or plaques with or without constitutional symptoms such as fever, malaise, and joint pain.

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For disability of hands and feet, the following World Health Organization (WHO) grading scale was used.
Grade 0: No anesthesia/no visible deformity.
Grade 1: Anesthesia present but no visible deformity.
Grade 2: Visible deformity/damage.

For disability of eyes also, the WHO grading scale was used.
Grade 0: No eye problems due to leprosy, no evidence of visual loss.
Grade1: Eye problem (corneal anesthesia, lagophthalmos, and iridocyclitis) due to leprosy present, but vision 6/60 or better, can count fingers at 6 m.
Grade 2: Severe visual impairment (vision worse than 6/60), inability to count fingers at 6 m.

Treatment was given according to the WHO recommendation to all patients.

RESULTS

In this 4 years study, we enrolled totally 212 patients. Year-wise total number of new cases ranged from 50 to 56 [Figure 1]. Maximum new cases were seen in 2019.

Out of 212 patients, 152 were male and 60 were female with male-female ratio of 2.5:1. Majority of cases were of the age group of 41–60 years (41%) followed by 21–40 years (36.3%), >60 years (14%), and 0–20 years (8.4%) [Table 1]. Seven patients were <15 years of age. Hence, child infection rate was 3.3%.

Total number of PB cases was 93 (43.8%) and MB cases were 119 (56.15%). The percentage MB cases in year 2016, 2017, 2018, and 2019 were 51.8% (28cases), 61.5% (32cases), 58% (29 cases), and 53.4% (30 cases), respectively [Figure 2].

One hundred and fourteen patients out of 212 (53.7%) were borderline tuberculoid type (BT) [Picture 1,2], 57 patients (26.8%) were borderline lepromatous (BL) [Picture 3,4], 14 patients (6.6%) were lepromatous leprosy (LL), 13 patients (6.1%) were tuberculoid leprosy, 8 patients (3.7%) were pure neuritic type, and 6 patients (2.8%) were histoid type [Picture 5] [Table 2].

Leprosy reactions were seen in 45 cases (21.2%) at the time of presentation, of which 37 cases (17.4%) were in Type 1 reaction [Picture 6] and 8 cases (3.8%) were in Type II reaction [Picture 7]. Year-wise comparison of Type I and II reaction is shown in Figure 3.

Grade 1 disability was seen in 46 cases (21.6%), Grade 2 disability was seen in 32 cases (15%), Grade 2 disability percentage in year 2016, 2017, 2018, and 2019 was 7.4% (4 cases), 17.3% (9 cases), 22% (11 cases), and 14.2% (8 cases), respectively [Figure 4].

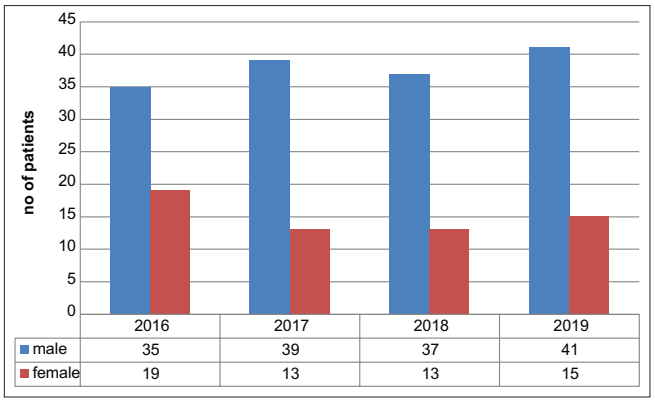


Figure 1: Sex-wise distribution

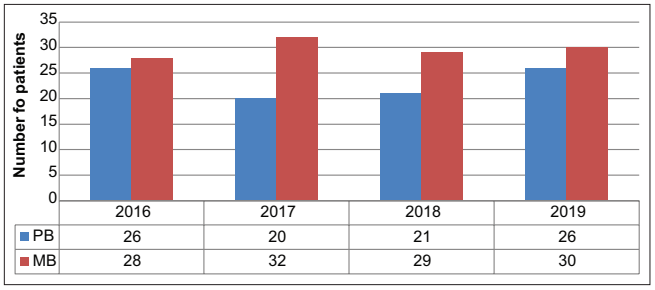


Figure 2: Paucibacillary versus multibacillary

Table 1: Age-wise distribution of patients

Age (years)	0–10		11–20		21–40		41–60		>60	
Sex	M	F	M	F	M	F	M	F	M	F
2016	-	1	3	1	13	10	14	7	5	-
2017	2	-	-	2	18	6	13	3	6	2
2018	-	-	3	3	14	2	15	6	5	2
2019	-	-	1	2	13	1	20	9	7	3

Among the deformity, ulnar claw hand was seen in 18 cases, total claw hand [Picture 8] in 6 cases, lagophthalmos [Picture 9] in 4 cases, foot drop in 2 cases, and auto-amputation of digits in 5 cases.

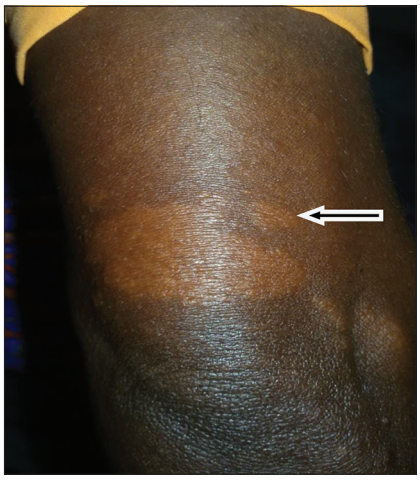
Nine patients gave a history of previous treatment for leprosy. Out of this, 6 patients were in BT spectrum. BL, pure neuritic, and histoid type were seen in one patient each.

DISCUSSION

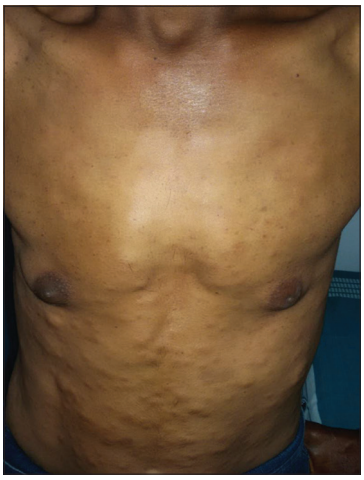
In our study, males outnumbered females with male-female ratio of 2.5:1. According to National Leprosy Eradication Program (NLEP) annual report 2016–2017, female patients were 39.17% which is more than our statistics of 28.3%.[2] Majority of cases belong to the age group of 41–60 years in our study followed by 21–40 years. However, a study by Thyvalappil *et al.*[3] states common age group affected as

Table 2: Clinical spectrum of disease

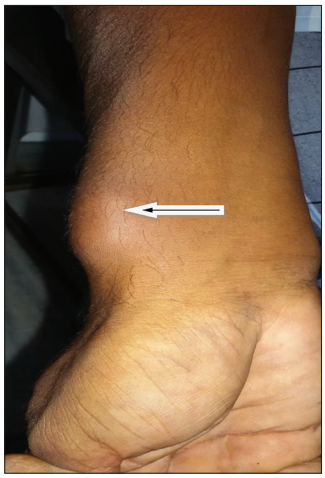
Year	Tuberculoid leprosy		Borderline tuberculoid		Borderline lepromatous		Lepromatous leprosy		Pure neuritic		Histoid	
	M	F	M	F	M	F	M	F	M	F	M	F
2016	5	2	17	12	9	3	1	1	-	-	3	1
2017	3	1	14	8	13	4	4	-	4	-	1	-
2018	-	-	24	11	10	2	3	-	-	-	-	-
2019	1	1	19	9	13	3	5	-	2	2	1	-



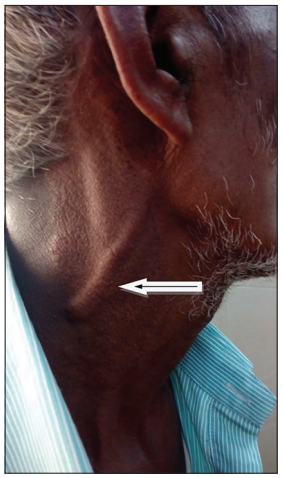
Picture 1: Borderline tuberculoid leprosy (well to ill-defined coppery red hypoanesthetic patch with satellite lesion [arrow] seen)



Picture 3: Borderline lepromatous leprosy (multiple asymmetrical smooth shiny papules and nodules with indefinite edge)



Picture 2: Radial cutaneous nerve thickening

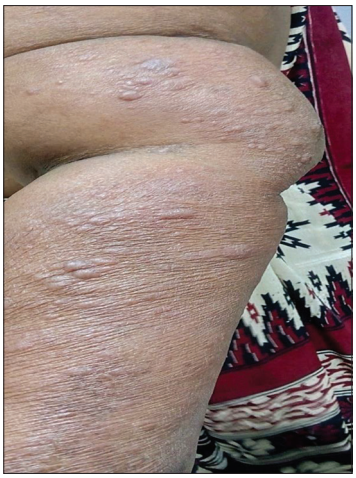


Picture 4: Greater auricular nerve thickening over the plaque lesion

20–40 years of age. Thus, the burden of the disease affects mainly the young productive male population of the society. Infection among <15 years of age was 3.3% in our study which is below the national level. It is because most of the children detected at school camp were given treatment by leprosy inspectors under the guidance of district officers.

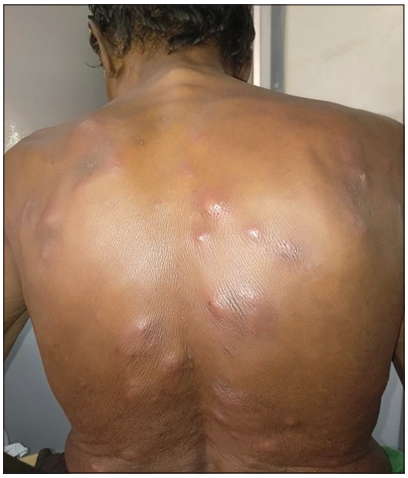
In this study, a total of 119 patients (56.15%) were MB patients as per the WHO classification. According to NLEP 2016–2017 annual report, proportion of MB cases in India was 49.57% which is less than our statistics.[2] Over these years, the number of MB cases did not show a decreasing trend. High proportion of MB cases indicates late reporting for diagnosis and treatment.[4] This may also be due to difficult to access to services or inadequate public awareness. Another reason is due to shift from active to passive case detection.

The most commonly encountered type of leprosy in our study was BT followed by BL and LL. This is consistent with the study by Relhan *et al.*, 2016.[5] To our surprise, the severe form of leprosy (lepromatous and BL) was less common in females than males. In pure neuritic type, ulnar nerve was commonly involved followed by lateral popliteal nerve.



Picture 5: Histoid leprosy (firm erythematous dome-shaped shiny nodules)

Picture 6: Type I reaction (erythema and edema over borderline tuberculoid lesion)



Picture 7: Type II reaction – erythema nodosum leprosum (multiple erythematous tender evanescent nodules over back)

Forty-five patients (21.2%) were in reactional state at the time of diagnosis, of which Type I reaction was more common

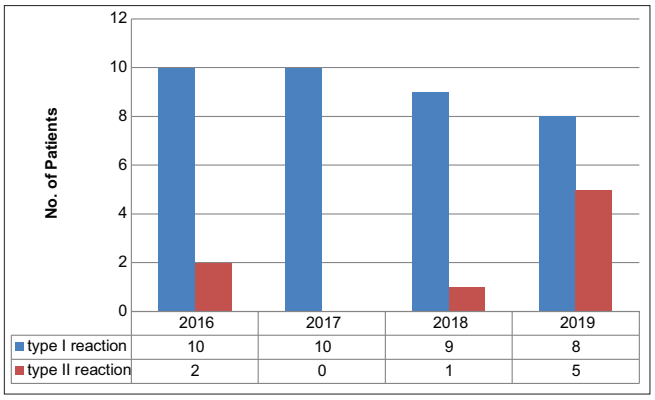


Figure 3: Comparison between Type I and Type II reaction

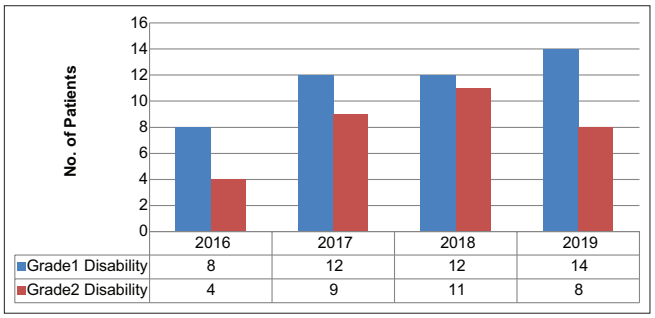


Figure 4: Disability severity

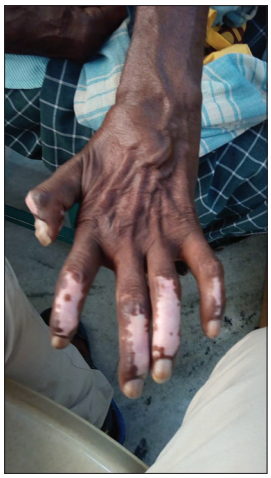
(17.4%). A study by Balagon *et al.* also shows a high proportion of patients with type I reaction at the time of diagnosis.[6]

Grade 2 disability (deformity) was seen in 32 cases (15% of total cases) in our study, whereas it was 34.78% in a study by Bhat and Chaitra.[7] Grade 2 disability also did not seem to decline over these years. Ulnar claw hand was the most common deformity noted. Persistence of high Grade 2 disability rate among new cases indicates that leprosy is being detected late and there may be hidden cases in the community.[8]

Those previously treated patients with new signs and symptoms of leprosy were mainly due to dapsone monotherapy or selection of incorrect multidrug therapy (MDT) regimen or poor patient compliance to treatment. Most of them were of BT spectrum and also responded well to restart of appropriate MDT regimen.

The knowledge about leprosy is poor among the affected individuals. Most of the cases came to us were referred by field health workers or referred from other departments for confirmation or incidentally we diagnosed as they attributed it to some other ailments.

Although there has been a significant reduction in prevalence of the disease worldwide since mid-1980s to elimination levels in December 2005, steady level of new cases indicates ongoing transmission.[9]



Picture 8: Total claw hand deformity

Picture 9: Lagophthalmos of the right eye

The WHO launched a 5-year "Global Leprosy Strategy 2016–2020" in April 2016 titled accelerating toward a leprosy-free world."[10]

It suggests,

1. Partnership with private sector including allopathic private practitioners for case detection/ referral, care, and social support of leprosy patients
2. Stop leprosy and its complications by strengthening patient and community awareness on leprosy, early case detection through special campaigns, ensuring prompt start and adherence to treatment, improving prevention and management of disabilities
3. Stop discrimination and promote inclusion by empowering leprosy affected persons in leprosy services, promoting access to social and financial support services.

CONCLUSION

In our study, males were more affected than females. Severity of the disease was less in females. BT type was commonly seen. The number of new cases, MB proportion, and deformity percentage did not show decreasing trend through the study years.

Based on this observation, we conclude that there is a need for wider awareness about signs and symptoms of leprosy and reactions among general health-care staffs as well as in the community to promote self-reporting, as well as early diagnosis and proper management of the disease and its complications in an integrated setting. "Care after Cure" that includes management of trophic ulcers and other long-term complications must also be addressed.

We also emphasize the urgent need for community based studies for devising appropriate strategy to break the chain in transmission of leprosy.

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Comparative Study of Split-Thickness Skin Grafting in Cases of Granulating Wounds with and without Scraping

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Abstract

Background: In the 21st century, prompt recovery and good functional outcome for patients with raw area depend largely on proper management of wound. The standard treatment of these wound is split-thickness skin grafting when wound becomes granulating. Some surgeons favor application of skin graft after scraping of granulation tissue, whereas others favor application of skin graft directly on the granulating wound which of the two methods offer a better take, better healing time and chances of regrafting was the objective of our study carried out in BJ Medical College and Civil Hospital, Ahmedabad.

Materials and Methods: This prospective comparative study was carried out on patients of the Department of Burns and Plastic Surgery, Civil Hospital and B. J. Medical College, Ahmedabad, Gujarat, India, from December 2017 to December 2019. A total of 30 adult subjects (both males and females) of age group (2–60 years) who were willing to participate were included in the study. The data were collected with a pro forma regarding patient, defect, and treatment-related parameters. All the details of the patients that were relevant to the study were collected during the pre-operative, surgical, and post-operative periods and during follow-up which was later analyzed.

Results: There were 18 (60.00%) males and 12 (40.00%) females included in the study and the mean age was 27.77 years. Male:female ratio was 1.5:1. Out of 30 patients, 23 (76.67%) having granulating wound due to burns injury, 2 (6.66%) patients having post-trauma granulating wound, and 5 (16.67%) patients having post-cellulitis granulating wound. Median area of wounds grafted in Group A was 163.40 ± 45.66 cm^2 (Mean ± SD) and in Group B was 161.80 ± 45.50 cm^2 (Mean ± SD) with $P = 0.45$. Mean graft uptake % in Group A was 87.00 ± 9.12 (Mean ± SD) and in Group B was 85.00 ± 10.14 (Mean ± SD). These differences were not statistically significant ($P = 0.25$). No statistically significant difference in graft uptake between two groups was noted when chronicity of the wounds was considered. About 60.00% of wound healed completely within 14 days in Group A against 46.67% in Group B. The mean duration of complete wound healing in Group A was 14.00 ± 3.06 (mean ± SD) and in Group B was 15.00 ± 3.56 (mean ± SD) which showed significant difference ($P = 0.0021$).

Conclusion: In scraped group, complete wound healing is faster than non-scraped group. The wounds with scraping had less discharge, required lesser number of dressings, and thus healed earlier with respect to control wounds. Scraping of granulation tissue was also associated with increased blood loss, more physiological insult to patient, increased operative time, and more requirement for blood transfusions. Because of increased loss of blood with scraping of the granulation tissue, perioperative risks to the patient due to blood loss after scraping of large granulating wound outweigh the advantage of marginally faster healing and comparable success rate of skin grafting. Therefore, it is not recommended to scrape the healthy granulation tissue before skin grafting.

Key words: Blood loss, Graft uptake, Non-scraping, Scraping, Split-thickness graft

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INTRODUCTION

Wound healing which is the stated goal of any wound management protocol has been described throughout recorded history, however, our understanding of its basic mechanisms has grown more in the past two decades than in the preceding two millennia. Nevertheless, poor wound

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healing remains a critical problem in our daily practice of surgery exerting a heavy toll on our patients as well as on the health-care system.[1] In the 21st century, prompt recovery and good functional outcome for such patients depend largely on proper management of wound. Perhaps, the greatest advances in burn care to date have been the institution of early surgical excision of the burn wound with immediate or delayed wound closure strategy to each patient.[2] Chronic wound for the purpose of this study meant a wound with skin loss which failed to heal or epithelialize on its own within 3 weeks from the date of injury. The standard treatment of these wound is split-thickness skin grafting when wound becomes granulating. The problem which arises now is how to apply skin graft on these granulating wounds. Opinion is divided on this issue, some surgeons favor application of skin graft after scraping of granulation tissue whereas others favor application of skin graft directly on the granulating wound. Despite its widespread use, there is little or no objective information about the outcomes of skin grafted wounds without knowing the exact time period. The actual length of time it takes for complete wound healing of skin grafted wounds has been reported by only few in the literature. There is very limited literature describing the impact of scraping of post-burn/trauma/cellulitis granulating wounds on take of split-thickness skin grafting and the length of time it takes to achieve complete wound healing in such cases which of the two methods offer a better take of skin grafts was the objective of our study.

MATERIALS AND METHODS

This prospective comparative study was carried out on patients of the Department of Burns and Plastic Surgery, Civil Hospital and B. J. Medical College, Ahmedabad, Gujarat, India, from December 2017 to December 2019. A total of 30 adult subjects (both males and females) of age group (2–60 years) who were willing to participate were included in the study.

Study Design

This was a prospective observational study.

Study Location

This was a tertiary care teaching hospital-based study done in the Department of Burns and Plastic Surgery, Civil Hospital and B. J. Medical College, Ahmedabad, Gujarat, India.

Study Duration

This study was from December 2017 to December 2019.

Sample Size

Thirty patients.

Inclusion Criteria

The following criteria were included in the study:

1. Age: 2–60 years
2. Post-burn or post-traumatic/cellulitis healthy granulation tissue
3. Raw area ≥200 cm^2 in dimension
4. Wounds of more than 3-week duration.

Exclusion Criteria

The following criteria were excluded from the study:

1. Age: >60 years or <2 years
2. Wounds of <3-week and >10-week duration
3. Patients with other medical illness (diabetes, hypertension, anemia [Hb <10 g%], malnutrition, bleeding disorder, and on anticoagulant, corticosteroid, and chemotherapy)
4. Wound swab culture positive for β-hemolytic streptococcal infection.

Procedure Methodology

Collection of data

The data were collected with a pro forma regarding patient, defect, and treatment-related parameters. All the details of the patients that were relevant to the study were collected during the pre-operative, surgical, and post-operative periods and during follow-up which was later analyzed.

Procedure

Both informed and written consents were taken about the procedure and the study on a preformed format. For each patient, specific data were collected on duration of wound, area of wound (measured with graph paper), and basic and specific investigation (e.g., wound swab culture and sensitivity, bleeding time, and clotting time). Area of wound was measured by cutting the sterile mackintosh sheet into shape of the wound then putting it over graph paper and outlining its border [Figure 1a]. The outlined area was then measured by counting the large and small squares of graph paper, and thus, raw area was calculated [Figure 1b]. The study was done by dividing the wound into two groups, Group A and Group B. In patients with single wound, Group A included approximate half area of wound in which granulation tissue was removed before skin grafting by scraping. Group B included remaining area of same wound where no scraping was done [Figure 1b]. In patients with multiple wounds, over different parts of body two wounds were selected as a Group A and Group B. Total wound area was cleaned with 5% povidone-iodine followed by saline wash. Complete scraping of granulation tissue was done by back of dissecting forceps/bard parker knife handle/scoop in Group A and hemostasis was achieved by adrenaline soaked gauzes, compression bandage, and electrocautery or ligation if required. Split skin grafts were meshed, applied, and secured by staples/sutures (same technique in both groups) and splint was given to provide best immobilization. Ratio of meshing was 1:2 or manual by pie crusting with surgical

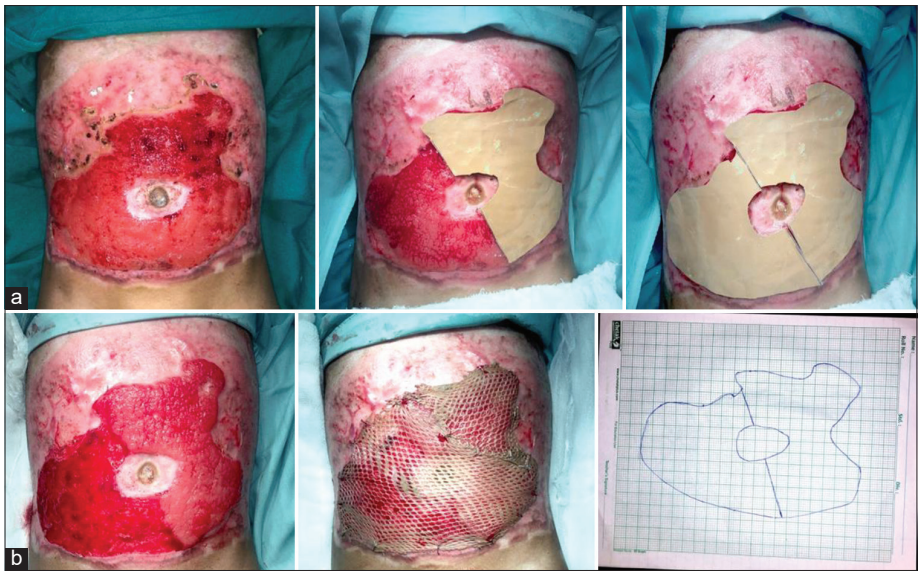


Figure 1: (a) Area of wound measured by cutting the sterile mackintosh sheet to shape of the wound. (b) Approximately half area of wound was scraped and rest served as control. It was grafted. Outlined area was measured by counting the large and small squares of graph paper

knife but same in test and control groups. Dressings were done after the 3rd, 5th, 7th, and 10th post-operative days and thereafter as required. Graft take was monitored on the 3rd, 7th, and 10th post-operative days. Percentage of graft take was measured using graph paper and calculated by subtracting the area of graft loss from estimated pre-operative raw area in both groups. Final outcome was decided by graft take as observed on the 10th day. Intraoperative blood loss was determined as the weight difference between the wet gauzes used in cleaning and achieving active hemostasis pre- and postoperatively. Pre-operative weight of gauzes used in this procedure was determined by weight difference between total wet gauzes taken preoperatively and remaining wet gauzes postoperatively in a bowl. All these weight measurements were done on same standard weighing machine. Time required for patient to be free from dressing and complete wound healing was calculated in both groups. Requirement of regrafting was also noted in both groups. The study was designed such as to enable us to achieve two important objectives. One was to eliminate the variables such as age, gender, duration of wounds, and nutrition that may affect graft uptake, by doing both the types of grafting on the same patient. The other was to remove any selection bias of patients by taking consecutive patients in the study.

Follow-up Procedure

The patient was followed up and dressings were done after the 3rd, 5th, 7th, and 10th post-operative days and thereafter as required. Graft take was monitored on the 3rd, 7th, and 10th post-operative days.

Assessment of Outcome

Percentage of graft take, percentage of intraoperative blood loss, time required for healing, and requirement for regrafting were noted and assessed statistically.

Table 1: Comparative distribution of area of wounds grafted

Area in cm²	Group A *n*=30 (%)	Group B *n*=30 (%)
100–150	14 (46.66)	15 (50.00)
150–200	10 (30.00)	10 (30.00)
>200	6 (20.00)	5 (16.00)

RESULTS

Thirty consecutive patients were studied. In these 30 patients, 13 had single wound which was divided into two parts (Group A and Group B) and 17 patients had wounds over different parts of body, presenting a milieu for an ideal comparative study.

There were 18 (60.00%) males and 12 (40.00%) females included in the study and the mean age was 27.77 years. Male:female ratio was 1.5:1. Out of 30 patients, 23 (76.67%) having granulating wound due to burns injury, 2 (6.66%) patients having post-trauma granulating wound, and 5 (16.67%) patients having post-cellulitis granulating wound. There was no statistically significant difference in the area of wounds grafted in two groups.

Table 1: Median area of wounds grafted in Group A was 163.40 ± 45.66 cm2 (Mean ± SD) and in Group B was 161.80 ± 45.50 cm2 (Mean ± SD) with P = 0.45.

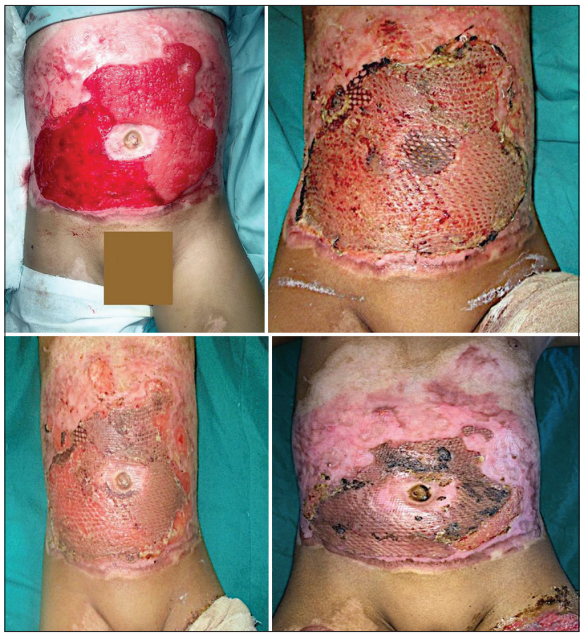
Figure 2: Mean graft uptake % in Group A was 87.00 ± 9.12 (Mean ± SD) and in Group B was 85.00 ±10.14 (Mean

± SD). These differences were not statistically significant ($P = 0.25$).

The average blood loss in Group A was 52.53 ml/100 cm^2 area of wounds, and in Group B, it was negligible. No grafts were lost due to seroma in both groups. No patient required regrafting in both groups.

Table 2: No statistically significant difference in graft uptake between two groups was noted when chronicity of the wounds was considered. About 60.00% of wound healed completely within 14 days in Group A against 46.67% in Group B.

Figure 3: The mean duration of complete wound healing in Group A was 14.00 ± 3.06 (mean ± SD) and in Group B was 15.00 ± 3.56 (mean ± SD) which showed significant difference (*P* value = 0.0021).



Patient photos: Post-burn wound abdomen:

a. Pre-operative right abdominal part scrapped, left abdominal part non-scrapped
b. Graft uptake on the 3rd post-operative day
c. Graft uptake on the 7th post-operative day
d. Graft uptake on the 14th day.

DISCUSSION

Any wounds with granulation tissue are managed by applying split skin graft. For improving skin grafting success rate, some surgeon prefers to scrape the granulation tissue but some surgeons consider it to be unnecessary. According to Brown and Mcdowell, if granulations are fresh, they can be grafted on directly, but if granulations are long standing and fibrous, they should be removed before applying graft.[3] This study was done to objectively evaluate the effect of scraping of granulation tissue on improvement of skin grafting success rate as compared to control where graft was applied directly without grafting. One prospective comparative study of skin grafting of chronic burn wounds with and without surgical removal of granulation tissue by Dhar *et al.* shows no significant difference in the comparative bacteriology, graft uptake, and cosmetic appearance of the grafts (mean graft uptake % in Group A was 83.74 ± 16.74 and in Group B was

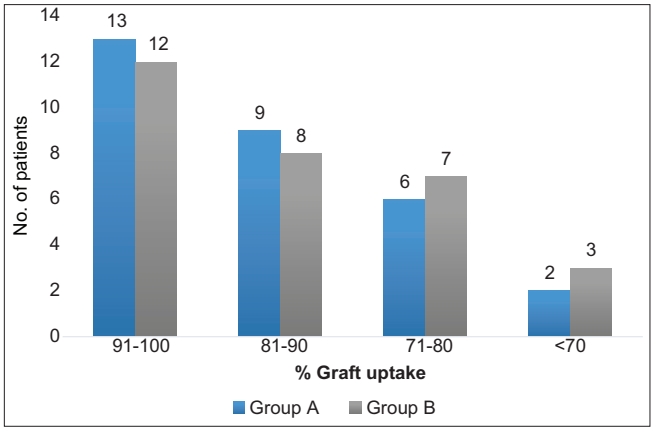


Figure 2: Comparative uptake of graft on the 10th post-operative day

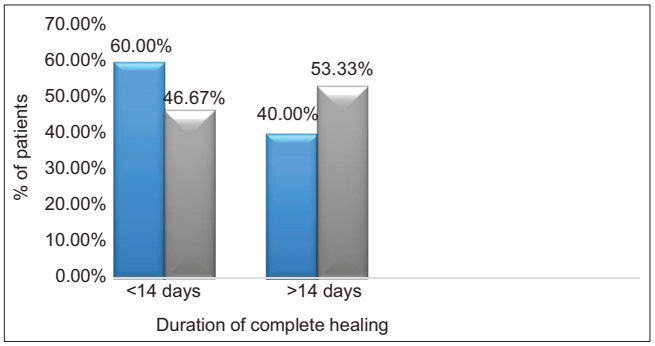


Figure 3: Comparative study of duration of complete healing

Table 2: Comparative distribution of graft uptake in relation to the chronicity of wounds

Chronicity (weeks)	% graft uptake	Group A	Group B	*P* value
3–6 weeks	81–100	16 (69.57%)	15 (65.22%)	*P*=0.63
(***n***=23)	<81	7 (30.43%)	8 (34.78%)	Non-significant
>6–10 weeks	81–100	5 (71.43%)	5 (71.43%)	*P*=0.51
(*n*=7)	<81	2 (28.57%)	2 (28.57%)	Non-significant

84.23 ± 18.90).[4] Our study was done by dividing the wound in two groups, Group A and Group B. Group A included approximate half area of wound in which granulation tissue was removed before skin grafting by scraping. Group B included remaining area of same wound where no scraping was done. The sample size was of 30 patients between the age group of 2 and 60 years. Mean graft uptake percentage in Group A was 87.00 ± 9.12 (Mean ± SD) and in Group B was 85.00 ± 10.14 (Mean ± SD). These differences were not statistically significant ($P = 0.25$). According to Lee *et al.*, estimation of blood loss using a gravimetric method is accurate and applicable in the clinical setting and provides surgeons with a simple and objective tool to evaluate intraoperative blood loss.[5] According to Bundy *et al.*, the mean blood loss for 1% of burn excised or split skin donor site harvested was 117 ml in adult cases and blood loss can also be expressed as a mean percentage of the patient's calculated total blood volume for each 1% burn excised or autograft harvested, giving figures of 2.6% for adults and 3.4% for children.[6] In our study, intraoperative blood loss was determined as the weight difference between the wet gauzes used in cleaning and achieving active hemostasis pre- and postoperatively. The average blood loss in Group A was 52.53 ml/100 cm^2 area of wounds and in Group B was minimal. Surgical removal of granulation tissue results in significant blood loss and adds to physiological and operative insult to already compromised and catabolic patient. There is also more oozing of tissue fluids after surgical removal (Group A) which also leads to protein loss.[7] Proteins in such patient are needed for building up body reserves in the form of hemoglobin and tissue proteins in addition to skin graft uptake. When the granulation tissue is not removed (Group B), there are minimal blood loss and minimal physiological insult and more secure hemostasis and proteins are thus conserved for graft uptake only as shown by Dhar *et al.*[4] According to Jewell *et al.*, most burn wounds after primary excision and skin grafting healed within 2 weeks and factors such as total body surface area burned, sex, age, graft type, and infection did not significantly influence time to complete wound healing.[8] Healthy granulation tissue fit for surgery is characterized by pink to red in color, finely granular in appearance, moist, epithelized margins, and minimal discharge, does not bleed easily on touch and free from β-hemolytic streptococci organisms.[9] It has an excellent blood supply but also contains debris, bacteria in the form of biofilm on their surface. Removal of granulation tissue decreases the load of bacteria resulting in improved graft uptake, less chances of infection, and early wound healing. In our study, 60.00% of wound healed completely within 14 days in Group A against 46.67 % in Group B. The mean duration of complete wound healing in Group A was 14.00 ± 3.06 (mean ± SD) and in Group B was 15.00 ± 3.56 (mean ± SD) which showed significant difference ($P = 0.0021$). These results are comparable to other studies in literature.

CONCLUSION

In this study, results show that success rate of skin graft uptake was comparable in both groups without significant difference. In scraped group, complete wound healing is faster than non-scraped group. The wounds with scraping had less discharge, required lesser number of dressings, and thus healed earlier with respect to control wounds. Scraping of granulation tissue was also associated with increased blood loss, more physiological insult to patient, increased operative time, and more requirement for blood transfusions. Because of increased loss of blood, scraping of the granulation tissue requires alertness on the part of attending doctors to detect hypotension which usually occurs suddenly. This causes more physiological instability in an already chronically ill patient if replacement by fluids and blood is not swift and adequate. Achieving hemostasis after scraping also requires time and efforts. Blood requirements for surgery and thus time and efforts required to arrange it can virtually be dispensed with if scraping is not done. Thus, perioperative risks to the patient due to blood loss after scraping of large granulating wound outweigh the advantage of marginally faster healing and comparable success rate of skin grafting. Therefore, it is not recommended to scrape the healthy granulation tissue before skin grafting.

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Original Article

A Prospective Comparative Study of Modified Biophysical Profile in Women with Normal Pregnancies and Oligohydramnios and their Perinatal Outcome

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Abstract

Aims and Objectives: The aim of the study was to compare role of modified BPP in predicting perinatal outcomes in oligohydramnios versus normal pregnancies.

Materials and Methods: This study was a prospective cohort study which consisted of 280 singleton pregnant women, out of which 140 were diagnosed with oligohydramnios. The patients were evaluated with a modified biophysical profile (MBPP) to analyze maternal and perinatal outcome.

Results: When MBPP is normal, it gives reassurance that the fetal status is good with the good perinatal outcome and decreased maternal morbidity. About 78.5% of patients had a normal vaginal delivery with 2% NICU admission and no neonatal death. When both parameters of MBPP are abnormal then there was an increased maternal and perinatal morbidity. About 88% had lower segment cesarean section (LSCS), with 65% having NICU admission and 2 neonatal death. Individually oligohydramnios patients having normal non-stress test also had relatively increased perinatal and maternal morbidity. In this study, 55% had LSCS and 16% NICU admission but no neonatal death. In broader outlook, oligohydramnios had adverse maternal and perinatal outcome when compared with low-risk pregnant women.

Conclusion: MBPP is an effective method of antepartum fetal surveillance test in oligohydramnios in predicting perinatal outcome.

Key words: Amniotic fluid index, Modified biophysical profile, Non-stress test, Oligohydramnios

INTRODUCTION

Pregnancy as a high-risk event was first recognized in 1901 by Ballantyne in his paper titled "A plea for pre-maternity hospital."[1]

Antenatal fetal surveillance is directed at identifying fetuses of the high-risk pregnancy group which is at risk of suffering intrauterine hypoxia with resultant damage, including death. The process of birth is the most dangerous journey an individual undertakes.[2]

A healthy Newborn is the goal of every expectant mother and her clinician. In India, about 0.75 million neonates die every year, the highest for any country in the world. The current perinatal mortality rate of India (2013) is 26 per 1000 births. It ranges from 16 per 1000 births in urban areas to 28 per 1000 births in rural areas.[3]

The various methods antepartum fetal testing according to ACOG 2014 are:[4]

- Subjective
  - Daily fetal movement count/Cardiff count to 10
  - Movements
  - Objective
  - Biophysical profile – (BPP)

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- Electronic fetal monitoring- non-stress test (NST)
- Contraction stress test
- Modified BPP – (MBPP)
- Umbilical and uterine artery Doppler ultrasound.

The American College of obstetrics and gynecology and the American Academy of Pediatrics (2016) have concluded that MBPP test as predictive of fetal well-being as other approaches to biophysical fetal surveillance.[5]

The original BPP by Manning *et al.*[6] needs 2 phase testing by ultrasound and external Doppler monitor to record the fetal heart rate (FHR). The complete BPP is more cumbersome, time-consuming, and is more expensive.

The MBPP suggested by Nageotte *et al.* combines NST and amniotic fluid index (AFI).[7]

Here NST is used as a short-term marker and AFI as a long-term marker of placental function. It is easier to perform and less time consuming than complete BPP.[8]

Amniotic fluid plays an important role in fetal health and development. Amniotic fluid allows for proper growth and development of the fetal lung and musculoskeletal system, has bacteriostatic, anti-inflammatory, and thermoregulatory functions.[9]

ACOG 2016 defines oligohydramnios is as AFI of 5 cm or less at term a single deepest pocket of amniotic fluid below 2 cm.[10]

Oligohydramnios can be associated with fetal congenital anomalies and intrauterine growth restriction (IUGR); it is usually proportional to the degree of IUGR and indicated placental dysfunction. Oligohydramnios can also cause asymmetrical fetal growth, contracture of joints, and hypoplasia of fetal lungs by decreasing the lung expansion due to compression of the fetal abdomen, which limits the movement of fetal diaphragm and decreases the flow of the amniotic fluid into and out of the fetal lung. It is associated with FHR abnormalities, cord compression, poor tolerance of the labor by the fetus, and low APGAR scores with poor perinatal outcome.[11]

Hence, in this study, MBPP is used as a method of antepartum surveillance test in oligohydramnios cases to study its effectiveness in predicting perinatal outcome.

MATERIALS AND METHODS

The present study was a prospective cohort study conducted in the department of obstetrics and gynecology of tertiary hospital from November 2017 to October 2020. Consecutive pregnant women of >36 weeks of gestation admitted to the hospital and giving consent to participate were included in the study. A detailed history including age, parity, body mass index (BMI), booking status, and obstetric history was noted. Thorough clinical examination was done. The volume of amniotic fluid was measured according to the four-quadrant technique described by Phelan *et al.*[12] With the patient in supine position, uterus was divided into four equal quadrants by two imaginary lines. An AFI of >5 was considered normal and ≤5 as abnormal. The last observation of MBPP was compared with the outcome of pregnancy.

The NST was performed with cardiotocogram. Recording of FHR, fetal movements, uterine contractions were done. The trace was considered as reactive if more than 2 fetal movements with the acceleration of more than or equal to 15 beats/min lasting for more than or equal to 15 s, with good beat-to-beat variability and no decelerations. If the reactive pattern was not recorded within 20 min period, the fetus was stimulated with the administration of a glucose-containing beverage and the test continued for another 20 min period. If there is no reactivity in this extended period, the trace was deemed non-reactive.

Patient's admission charts, labor ward records, operating notes, and nursery sheets were reviewed. Information regarding trial of labor was available from labor ward records. Operative findings were noted down from operative notes and neonatal data were collected from nursery sheets. Indication for CS noted down. Mode and indication of delivery were recorded. Nature of amniotic fluid was noted and classified into meconium stained, clear, absent, and blood mixed.

Inclusion Criteria Cases

The following criteria were included in the study:

- All pregnant women diagnosed with oligohydramnios confirmed by ultrasound after 36 weeks
- Primigravida and multigravida will be included
- Patients who are booked or unbooked
- Singleton pregnancy with cephalic presentation
- Non-anomalous fetus
- Patients conceiving through assisted reproductive technology techniques.

Controls

Normal singleton pregnant women with normal AFI and normal NST with no risk factors such as GDM, hypertension, pre-eclampsia, eclampsia, heart disease, thyroid disorders, placenta abnormalities, previous lower segment cesarean section (LSCS), chronic connective tissue disorders, cholestasis, asthma, and autoimmune disorders.

Exclusion Criteria

The following criteria were excluded from the study:

- Pregnant women with gestational age <36 weeks
- Multiple pregnancies
- Pregnant women with risk factors such as eclampsia, GDM, asthma, and autoimmune disorders.

Sample Size

Around 4000 cases come to the hospital per year, out of which 80–85 patients had oligohydramnios over a period of 5 years. Now using Raosoft formula with a 95% confidence interval (CI) and 5% margin error, the sample size is 140 for 2 years.

$$y = Z\,[c/100]\,2r\,[100-r]$$

$$n = Ny\,[N-1]\,E\,2+y$$

$$E = \text{sqrt}\,[(N-n)y/n(N-1)]$$

Sample size n
Margin of error E (5%)
N is the population size
R is the fraction of response
Z [c/100] is the critical value for CI c (95%).

Total number of patients with confirmed oligohydramnios was 140. Among them, 80 patients had reactive NST and the rest 60 patients had non-reactive NST. These were considered as cases. The rest did not fulfill the inclusion criteria.

For every single case of oligohydramnios, one case of normal MBPP was selected after fulfilling inclusion criteria to compare the obstetric and perinatal outcome.

Total 140 cases were selected out of which:

- 60 cases which had oligohydramnios with non-reactive NST, termed as Group I
- 80 cases with oligohydramnios who had reactive NST were termed as Group II
- 140 controls with normal AFI and normal NST termed as Group III.

Data on neonatal outcome under the following parameters noted:

- Respiratory distress at birth
- Asphyxia (APGAR score at 1 min and 5 min)
- NICU admission
- Birth weight
- Neonatal death
- Need for resuscitation.

The perinatal outcome is considered abnormal[13] if any of the following was present:

1. Antepartum/Intrapartum fetal distress
2. Apgar score at 5 min <7
3. Admission in NICU for >24 h
4. Perinatal death.

All the five criteria of APGAR scoring[14] were taken as shown in table and the following analysis of APGAR score was made.

Apgar score of 7–10 normal, 6–4 mild asphyxia, 0–3 severe asphyxia.

Fetal distress was mainly evaluated in terms of fetal bradycardia, tachycardia, repetitive variable decelerations, and late decelerations.[15]

RESULTS AND OBSERVATIONS

A total of 280 pregnant women were included in the study and the following observations were made.

No significant difference was seen in the age distribution between Group I, II, and III ($P > 0.05$). Mean value of age of patients in Group I was 27.83 ± 3.85 years, in Group II was 27.86 ± 3.77 years, and in Group III was 28.06 ± 4.58 years.

No significant difference was seen in the BMI between the three groups ($P > 0.05$). Mean value of BMI in Group I was 25 ± 2.56 kg/m^2, in Group II was 25.08 ± 2.34 kg/m^2, and in Group III was 25.02 ± 1.69 kg/m^2 without any significant difference between them.

No significant difference was seen in the gravida and parity between Group I, Group II, and Group III ($P > 0.05$). Majority of patients in all the groups were multigravida; 66.67% in Group I, 71.25% in Group II, and 70.71% in Group III.

Gestational age, according to last menstrual period (LMP) and ultrasonography (USG), was significantly different

Signs	0	1	2
Respiratory effort	Absent	Slow, irregular	Good cry
Heart rate	Absent	Slow, below 100	>100
Muscle tone	Flaccid	flexion of extremities	Active body movements
Reflex irritability	No response	Minimum response to stimulation	Prompt response to stimulation
Color	Pale	Pink body, blue extremities	Complete pink

between the three groups (*P* value <.05). Mean value of gestational age on LMP and on USG was significantly higher in Group III followed by Group II and was significantly lower in Group I [Tables 1-8].

Significant difference was seen in the mode of delivery between Group I, Group II, and III ($P < 0.05$) Mode of delivery was LSCS in 88.33% of the patients in Group I as compared to 55% and19.29% of patients in Group II and Group III, respectively.

A significant difference was seen amniotic fluid between the groups ($P < 0.05$). About 97.14% of the patients in Group III had clear amniotic fluid as compared to 71.25% in Group II and 26.67% in Group I. On the other hand, 38.33% of the patients had moisture sensitivity level (MSL) in Group I as compared to 8.75% in Group II and 2.14% in Group III.

A significant difference was seen in the indication between all the three groups ($P < 0.0001$) 57.86% of the patients in Group III had spontaneous labor as compared to 22.50% in Group II and 0% in Group I. On the other hand, around 50% of patients had either failed induction of labor/fetal distress in Group I.

A significant difference was seen in the distribution of mode of delivery between Group I+II as compared to Group III ($P < 0.05$), 78.57% of patients had normal vaginal delivery in Group III as compared to 26.43% of patients in Group I +II. Hence, it can be concluded that patients in Group III had significantly higher chances of normal delivery as compared to Group I+II [Tables 9-15].

A significant difference was seen in the distribution of nature of amniotic fluid between Group I+II as compared to Group III ($P < 0.05$). About 97.14% of patients had clear liquor in Group III as compared to 52.14% of patients in Group I+II.

A significant difference was seen in the indication of delivery between Group I+II as compared to Group III ($P < 0.05$). About 57.86% of patients had spontaneous labor in Group III as compared to 12.86% of patients in Group I +II.

A significant difference was seen in the distribution of the APGAR score between the two Group I+II versus Group III ($P < 0.05$). About 34.29% of the patients had APGAR score <7 at 1 min and 25% of the patients had APGAR score <7 at 5 min in Group I+II as compared to 1.43% and 0.71% in Group III, respectively.

A significant difference was seen in the distribution of the birth weight between Group I+II and III ($P < 0.05$). About

Table 1: Demographic distribution of study participants

Age distribution in years	Group			Total	*P* value	I versus II	I versus III	II versus III	Key
	I (*n*=60)	II (*n*=80)	III (*n*=140)						
20-25	19 (31.67%)	25 (31.25%)	43 (30.71%)	87 (31.07%)	0.544*	0.983*	0.356*	0.382*	*Chi-square test
26–30	29 (48.33%)	38 (47.50%)	56 (40.00%)	123 (43.93%)					#Kruskal–Wallis test
31–35	12 (20.00%)	17 (21.25%)	41 (29.29%)	70 (25.00%)					@Mann–Whitney test
Mean ± Std. dev.	27.83±3.85	27.86±3.77	28.06±4.58	27.95±4.20	0.623#	0.84@	0.414@	0.448@	
Median (IQR)	28 (25–30)	29.5 (27–30)	30(28–32)	29(24.5–30.5)					
Body mass index (kg/m^2)									
Mean ± Std. dev.	25±2.56	25.08±2.34	25.02±1.69		0.913#	0.795*	0.652*	0.942*	#Kruskal–Wallis test
Median (IQR)	25(23–26)	25(24–26)	25(24–26)						*Mann–Whitney test
Gravida									
Primi	20 (33.33%)	23 (28.75%)	41 (29.29%)	84 (30.00%)	0.814	0.692	0.688	0.944	*Chi-square test
Multi	40 (66.67%)	57 (71.25%)	99 (70.71%)	196 (70.00%)					
Parity									
0	23 (38.33%)	24 (30.00%)	42 (30.00%)	89 (31.79%)	0.593	0.264	0.457	0.781	*Chi-square test
1	27 (45.00%)	31 (38.75%)	62 (44.29%)	120 (42.86%)					
2	9 (15.00%)	23 (28.75%)	34 (24.29%)	66 (23.57%)					
3	1 (1.67%)	2 (2.50%)	2 (1.43%)	5 (1.79%)					
Gestational age in weeks									
Last menstrual period Mean ± Std. dev.	37.6±1.61	38.45±1.49	39.28±1.27		<0.0001*	0.001#	<.0001#	0.0001#	*Kruskal–Wallis test
Last menstrual period Median (IQR)	37 (36.143–38)	38 (37–40)	39.29 (38.143–40)						#Mann–Whitney test
Ultrasonography Mean±Std. dev.	35.7±2.37	36.77±2.21	37.97±1.33		<0.0001*	0.003#	<0.0001#	0.0001#	
Ultrasonography median (IQR)	36 (34–37.429)	37.07 (36–38.214)	38 (37.143–39)						

Table 2: Comparison of mode of delivery between Group I, II, and III

Mode of delivery	Group (%)			Total (%)	*P* value	I versus II	I versus III	II versus III
	I (*n*=60)	II (*n*=80)	III (*n*=140)					
LSCS	53 (88.33)	44 (55.00)	27 (19.29)	124 (44.29)	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Normal vaginal delivery	5 (8.33)	32 (40.00)	110 (78.57)	147 (52.50)				
vaginal delivery with forceps	2 (3.33)	4 (5.00)	3 (2.14)	9 (3.21)				
Total	60 (100.00)	80 (100.00)	140 (100.00)	280 (100.00)				

*Chi-square test. LSCS: Lower segment cesarean section

Table 3: Comparison of nature of amniotic fluid between Group I, II, and III

Nature of amniotic fluid	Group (%)			Total	*P* value	I versus II	I versus III	II versus III
	I (*n*=60)	II (*n*=80)	III (*n*=140)					
Absent	20 (33.33)	13 (16.25)	0 (0.00)	33 (11.79)	<.0001*	<.0001*	<.0001*	<.0001*
Blood mixed	1 (1.67)	3 (3.75)	1 (0.71)	5 (1.79)				
Clear	16 (26.67)	57 (71.25)	136 (97.14)	209 (74.64)				
Moisture sensitivity level	23 (38.33)	7 (8.75)	3 (2.14)	33 (11.79)				
Total	60 (100.00)	80 (100.00)	140 (100.00)	280 (100.00)				

*Chi-square test

Table 4: Comparison of indications of delivery between Group I, II, and III

Indications	Group (%)			Total (%)	*P* value	I versus II	I versus III	II versus III
	I (*n*=60)	II (*n*=80)	III (*n*=140)					
2nd stage arrest	0 (0.00)	4 (5.00)	5 (3.57)	9 (3.21)	<0.0001*	0.001*	<0.0001*	<0.0001*
Abruption placenta	2 (3.33)	3 (3.75)	1 (0.71)	6 (2.14)				
Chorioamnionitis	1 (1.67)	1 (1.25)	0 (0.00)	2 (0.71)				
Failed induction of labor	14 (23.33)	19 (23.75)	13 (9.29)	46 (16.43)				
Fetal distress	16 (26.67)	14 (17.50)	7 (5.00)	37 (13.21)				
Forceps delivery	0 (0.00)	0 (0.00)	2 (1.43)	2 (0.71)				
Induction of labor	2 (3.33)	7 (8.75)	7 (5.00)	16 (5.71)				
Induction of labor for Doppler changes	2 (3.33)	1 (1.25)	0 (0.00)	3 (1.07)				
Intrauterine growth restriction with reverse Doppler	3 (5.00)	0 (0.00)	0 (0.00)	3 (1.07)				
Maternal request	2 (3.33)	0 (0.00)	1 (0.71)	3 (1.07)				
NPOL	7 (11.67)	3 (3.75)	3 (2.14)	13 (4.64)				
Pre-labor rupture of membranes	11 (18.33)	10 (12.50)	20 (14.29)	41 (14.64)				
Spontaneous labor	0 (0.00)	18 (22.50)	81 (57.86)	99 (35.36)				
Total	60 (100.00)	80 (100.00)	140 (100.00)	280 (100.00)				

*Chi-square test

Table 5: Comparison of APGAR between Group I, II, and III

APGAR	Group			Total	*P* value	I versus II	I versus III	II versus III
	I (*n*=60)	II (*n*=80)	III (*n*=140)					
At 1 min								
<7	33 (55.00%)	15 (18.75%)	2 (1.43%)	50 (17.86%)	<0.0001*	<0.0001*	<0.0001$	<0.0001$
≥7	27 (45.00%)	65 (81.25%)	138 (98.57%)	230 (82.14%)				
Mean ± Std. dev.	6.48±1.26	7.6±1.19	8.19±0.75	7.65±1.2	<0.0001#	<0.0001@	<0.0001@	0.0004@
Median (IQR)	6 (6–7)	8 (7–9)	8 (8–9)	8 (7–9)				
At 5 min								
<7	28 (46.67%)	7 (8.75%)	1 (0.71%)	36 (12.86%)	<0.0001*	<0.0001*	<0.0001$	0.004$
≥7	32 (53.33%)	73 (91.25%)	139 (99.29%)	244 (87.14%)				
Mean±Std. dev.	7.08±1.57	8.2 ± 0.97	8.79±0.75	8.26±1.23	<0.0001#	<0.0001@	<0.0001@	<0.0001@
Median (IQR)	7 (6–8)	8 (8–9)	9 (8–9)	8.5 (8–9)				

*Chi-square test, $Fisher's exact test, #Kruskal–Wallis test, @Mann–Whitney test

23.57% of the patients in Group I+II had birth weight ≤2500 g as compared to only 0% in Group III. It can be concluded that the birth weight was significantly lower in Group I+II as compared to Group III.

Table 6: Comparison of birth weight between Group I, II, and III

Birth weight (in grams)	Group			Total	*P* value	I versus II	I versus III	II versus III
	I (*n*=60)	II (*n*=80)	III (*n*=140)					
≤2500	22 (36.67%)	11 (13.75%)	0 (0.00%)	33 (11.79%)	<.0001*	0.002*	<0.0001#	<0.0001#
>2500	38 (63.33%)	69 (86.25%)	140 (100.00%)	247 (88.21%)				
Mean±Std. dev.	2515.95±448.41	2767.41±335.28	2921.65±159.73	2790.65±334.75	<0.0001@	0.0001$	<0.0001$	0.0001$
Median (IQR)	2678 (2285–2835)	2820 (2679–2956)	2901 (2807–2990)	2899 (2700–2980)				

*Chi-square test, #Fisher's exact test, @Kruskal–Wallis test, $Mann–Whitney test

Table 7: Comparison of NICU admission >24 h between Group I, II, and III

NICU admission >24 h	Group (%)			Total (%)	*P* value	I versus II	I versus III	II versus III
	I (*n*=60)	II (*n*=80)	III (*n*=140)					
No	21 (35.00)	67 (83.75)	137 (97.86)	225 (80.36)	<0.0001*	<0.0001*	<0.0001#	0.0002#
Yes	39 (65.00)	13 (16.25)	3 (2.14)	55 (19.64)				
Total	60 (100.00)	80 (100.00)	140 (100.00)	280 (100.00)				

*Chi-square test, #Fisher's exact test

Table 8: Comparison of neonatal death between Group I, II, and III

Neonatal death	Group (%)			Total (%)	I versus II	I versus III	II versus III
	I (*n*=60)	II (*n*=80)	III (*n*=140)				
No	58 (96.67)	80 (100.00)	140 (100.00)	278 (99.29)	0.182*	0.089*	-
Yes	2 (3.33)	0 (0.00)	0 (0.00)	2 (0.71)			
Total	60 (100.00)	80 (100.00)	140 (100.00)	280 (100.00)			

*Fisher's exact test

Table 9: Comparison of mode of delivery between Groups I+II and III

Mode of delivery	Group (%)		Total (%)	*P* value
	I+II (*n*=140)	III (*n*=140)		
LSCS	97 (69.29)	27 (19.29)	124 (44.29)	<0.0001
Normal vaginal delivery	37 (26.43)	110 (78.57)	147 (52.50)	
Vaginal delivery with forceps	6 (4.29)	3 (2.14)	9 (3.21)	
Total	140 (100.00)	140 (100.00)	280 (100.00)	

LSCS: Lower segment cesarean section

Table 10: Comparison of nature of amniotic fluid between Groups I+II and III

Nature of amniotic fluid	Group (%)		Total (%)	*P* value
	I+II (*n*=140)	III (*n*=140)		
Absent	33 (23.57)	0 (0.00)	33 (11.79)	<.0001
Blood mixed	4 (2.86)	1 (0.71)	5 (1.79)	
Clear	73 (52.14)	136 (97.14)	209 (74.64)	
Moisture sensitivity level	30 (21.43)	3 (2.14)	33 (11.79)	
Total	140 (100.00)	140 (100.00)	280 (100.00)	

A significant difference was seen in the NICU admission distribution between Group I+II and III ($P < 0.05$). About 37.14% of patients in Group I+II required NICU admission as compared to only 2.14% of the patients in Group III.

No significant difference was seen in the distribution of the neonatal death between Group I+II as compared to Group III ($P > 0.05$). Neonatal death was seen in only 1.43% of the patients in Group I+II and 0% in Group III.

DISCUSSION

Oligohydramnios pregnancies need to be identified so that appropriate surveillance and timely intervention can be employed and thus bring down the rate of perinatal morbidity and mortality.[11]

The best method is the one, which aims at identifying the fetus, which is at risk but still in an uncompromised state and requires immediate intervention.

Table 11: Comparison of indication of delivery between Groups I+II and III

Indications	Group (%)		Total (%)	*P* value
	I+II (*n*=140)	III (*n*=140)		
2nd stage arrest	4 (2.86)	5 (3.57)	9 (3.21)	<.0001
Abruptio placenta	5 (3.57)	1 (0.71)	6 (2.14)	
Chorioamnionitis	2 (1.43)	0 (0.00)	2 (0.71)	
Failed induction of labor	33 (23.57)	13 (9.29)	46 (16.43)	
Fetal distress	30 (21.43)	7 (5.00)	37 (13.21)	
Forceps delivery	0 (0.00)	2 (1.43)	2 (0.71)	
Induction of labor	9 (6.43)	7 (5.00)	16 (5.71)	
Induction of labor with Doppler changes	3 (2.14)	0 (0.00)	3 (1.07)	
Intrauterine growth restriction with reverse Doppler	3 (2.14)	0 (0.00)	3 (1.07)	
Maternal request	2 (1.43)	1 (0.71)	3 (1.07)	
NPOL	10 (7.14)	3 (2.14)	13 (4.64)	
Pre-labor rupture of membranes	21 (15.00)	20 (14.29)	41 (14.64)	
Spontaneous labor	18 (12.86)	81 (57.86)	99 (35.36)	
Total	140 (100.00)	140 (100.00)	280 (100.00)	

Table 12: Comparison of APGAR between Groups I+II and III

APGAR	Group		Total	*P* value
	I+II (*n*=140)	III (*n*=140)		
At 1 min				
<7	48 (34.29%)	2 (1.43%)	50 (17.86%)	<0.0001*
≥7	92 (65.71%)	138 (98.57%)	230 (82.14%)	
Mean±Std dev	7.12±1.33	8.19±0.75	7.65±1.2	<0.0001#
Median (IQR)	7 (6–8)	8 (8–9)	8 (7–9)	
At 5 min				
<7	35 (25.00%)	1 (0.71%)	36 (12.86%)	<0.0001*
≥7	105 (75.00%)	139 (99.29%)	244 (87.14%)	
Mean±Std dev	7.72±1.37	8.79±0.75	8.26±1.23	<0.0001#
Median (IQR)	8 (6.500–9)	9 (8–9)	8.5 (8–9)	

*Fisher's Exact test. #Mann–Whitney test

Table 13: Comparison of birth weight between Groups I+II and III

Birth weight (in grams)	Group		Total	*P* value
	I+II (*n*=140)	III (*n*=140)		
≤2500	33 (23.57%)	0 (0.00%)	33 (11.79%)	<0.0001*
>2500	107 (76.43%)	140 (100.00%)	247 (88.21%)	
Mean ± Std. dev.	2659.64 ± 405.99	2921.65±159.73	2790.65 ± 334.75	<0.0001#
Median (IQR)	2800 (2560–2901)	2901(2807–2990)	2899(2700 - 2980)	

*Fisher's Exact test, #Mann–Whitney test

Table 14: Comparison of NICU admission >24 h between Group I+II and III

NICU admission >24 h	Group (%)		Total (%)	*P* value
	I+II (n=140)	III (n=140)		
No	88 (62.86)	137 (97.86)	225 (80.36)	<0.0001*
Yes	52 (37.14)	3 (2.14)	55 (19.64)	
Total	140 (100.00)	140 (100.00)	280 (100.00)	

*Fisher's exact test

The incidence of potentially preventable perinatal death following a negative MBPP was <1/1000 tested high-risk pregnancies.[16]

During the period of study, the total number of deliveries was 4000 per year. Among them, 140 patients (1.7%) were oligohydramnios at term.

In the present study, the mean age group was 26–30 years. Group 1 was 27.83 years, Group 2 and Group 3 were 27.86 years and 28.06 years, respectively, but the difference in mean age was not statistically significant ($P > 0.05$). A study by Raparthy and Sunithae[11] showed most of the patients belonging to the age group between 21 and 25 years (53%).

Table 15: Comparison of neonatal death between Groups I+II and III

Neonatal death	Group (%)		Total (%)	*P* value
	I+II (*n*=140)	III (*n*=140)		
No	138 (98.57)	140 (100.00)	278 (99.29)	0.498*
Yes	2 (1.43)	0 (0.00)	2 (0.71)	
Total	140 (100.00)	140 (100.00)	280 (100.00)	

*Fisher's exact test

The majority of patients were multigravida in Group I, II, and III in the present study, 66.67%, 71.25%, and 70.71%, respectively. This was not statistically significant ($P = 0.81$). In a study by Sowmya,[17] majority patients were primigravida (46%). Parity is not significantly related to MBPP score in all groups of patients.

Mean gestational age was 37.6, 38.4, and 39.2 weeks in Group I, II, and III according to LMP. Twenty-two patients in Group I and 18 patients in Group II had IUGR, which was confirmed by USG. The gestational age among the three groups was comparable was statistically significant. A similar study by Sowmya[17] in her study stated majority gestational age was 36–37 weeks (43%).

In the present study, 88% of patients had C section when both the parameters of MBPP (Group I) was abnormal compared to 55% when NST was reactive (Group II) and 19.29% when both parameters were normal (Group III). This was statistically significant with $P < 0.0001$. Similar findings were quoted by Raparthy and Sunithae[11] that the mode of delivery in the study group with respect to the last MBPP result showed that when MBPP was normal with respect to both parameters (37 cases), the incidence of LSCS and vaginal delivery among these were 11 (29.72%) and 26 (70.27%), respectively. When the MBPP is abnormal with respect to both parameters (4 cases), all the 4 (100%) had LSCS. When the MBPP is abnormal with respect to AFI (3 cases), 1 case (33.33%) had LSCS and 2 cases (66.66%) had vaginal delivery.

In a broader outlook, patients with oligohydramnios (Group I + II) had had a high rate of LSCS (69.29%) compared to normal low-risk term pregnancies (19.2%). Similarly, Dalal and Malhotra,[18] in his study, quoted 41% underwent LSCS.

In the present study, during delivery among 60 patients with both abnormal MBPP (Group I), 38.3% patients had MSL and 33% had absent amniotic fluid compared to 8% and 16%, respectively, in Group II. When both parameters (Group III) were normal, 2% had MSL. This was statistically significant ($P < 0.0001$). In a study by Swetatara and Rashmi,[19] all 9 (100%) cases with both parameters abnormal had thick meconium-stained liquor and 3 (4%) cases of the 68 cases with both normal parameters had thick meconium stained liquor. Thus, it is seen that the incidence of perinatal morbidity with respect to meconium is increased when both MBPP parameters were abnormal, and more so when NST abnormal compared to AFI abnormal when individual parameters were considered.

Rabie *et al.*[20] stated that there was no difference in the rate of MSL in isolated oligohydramnios but increased the chance of meconium aspiration syndrome.

In this study, in oligohydramnios, 21.43% and 23.57% had MSL and absent liquor, respectively. A similar finding was quoted by Sriya and Singhai[21] who had meconium-stained liquor about 54% in her study.

In the present study, among all indications of delivery, it was observed that fetal distress was most common, with 26.67% when both parameters of MBPP were abnormal, of which all cases were delivered by LSCS, compared to 14%, when NST was reactive (Group II). In Group III, 7% of patients had fetal distress. 23.3% had failed induction in Group I, and this was seen even in patients under Group II (23%) compared to 9% in controls (Group III). Around 11% in Group I did not progress in labor compared to 3% in controls (Group II), thereby suggesting liquor playing an important role in induction and progress of labor. Spontaneous labor was more common in Group III (57%) compared to 18% in Group II and none of the patients were observed to undergo spontaneous labor when both the parameters were abnormal (Group I). These findings were statistically significant ($P < 0.0001$). A study by Maurya and Kushwah[22] supported the above observations, stated that number of LSCS for fetal distress was more, that is, 7 (23.3%) when NST pattern was non-reactive as compared to reactive NST pattern, that is, 6 cases (7.5%).

In the present study, a total (21.43%) of patients with oligohydramnios had a higher rate of fetal distress compared to 7% in normal low-risk pregnancies, similarly naval physical and oceanographic laboratory were more common in oligohydramnios (7.14%) compared to normal pregnancies (2.14%). A similar finding was stated by Das[23] in his study that out of 25 women (50%) that developed fetal

distress in the study group, 22 (44%) of them underwent C section and 3 (6%) had a forceps delivery.

In the present study, low birth weight was seen higher in Group I (36.67%) compared to Group II (13.75%). None of the babies in Group III were low birth weight. This was statistically significant ($P < 0.05$). This may be because IUGR is associated with oligohydramnios. Similar studies were quoted by Maurya and Kushwah,[22] 23.3% had birth weight <2 kg. When NST was non-reactive and (11.3%) had birth weight <2 kg when NST was reactive.

In a present study among oligohydramnios, 23.5% had low birth weight and no low birth babies were seen in the control group. This was statistically significant ($P < 0.05$). A study by Shah *et al.*[24] stated 48% of oligohydramnios was associated with low birth weight babies.

Neonatal complications were analyzed on several parameters, including APGAR at 1 min and 5 mins with a score 6 or less at 5 min being associated with bad prognosis and NICU admission.

In the present study, APGAR <7 at 1 min in Group I, II, and III was (55%, 18.7%, and 1.4%) respectively and at 5 min (46.7%, 8.7%, and 0.71%) respectively, thereby suggesting low and no improvement in APGAR score at 5 min in babies of Group I compared to II and III. This was statistically significant ($P < 0.0001$). Sowmya[17] stated that 3 out of 5 patients had APGAR <7 when MBPP was abnormal.

Overall, patients with oligohydramnios had lower APGAR at 1 and 5 min (34.2% and 25%), respectively, when compared to controls (1.43% and 0.71%), 1 respectively. Similarly, in a study by Mohammed and Jahangir,[25] APGAR <7 at 1 min and 5 min were 38% and 10%.

NICU admission rate was significantly higher in babies born in Group I ($P < 0.05$). In the present study, NICU admission rate was 65% compared to 16.25% in Group II and 2.14% in Group III. Raparthy and Sunithae,[11] in her study suggested, in the last MBPP, when both the parameters were abnormal, 100% of the cases had NICU admission, whereas when only AFI is abnormal, 75% of the cases had NICU admission, thereby suggesting MBPP as a predictor of perinatal morbidity.

Oligohydramnios itself is a predisposing factor for rising NICU admission. In this study, 37.14 % babies were admitted in NICU compared to 2.14% in Group III. In a study by Shah *et al.*,[24] a total of 41% of newborns were admitted in the neonatal ward (NICU) for morbidities.

Despite the best possible interventions and care, 2 newborns in Group I died. Both due to severe birth asphyxia with absent liquor, whereas no neonatal deaths were seen in Group II and Group III. This was not statistically significant ($P = 0.1$). Raparthy and Sunithae,[11] in her study, observed that there were 2 (3.33%) perinatal mortalities.

Overall in the present study, both neonatal deaths occurred in patients in oligohydramnios babies. Both the death was statistically non-significant ($P = 0.4$). Das[23] stated in his study that there were 4 deaths in oligohydramnios group, which was non-significant ($P = 0.1$).

CONCLUSION

MBPP is an easier, less time consuming, cost-effective, and patient compliant test.

- When MBPP is abnormal, it indicates that the fetus may be compromised or increased incidence of perinatal morbidity as well as mortality
- When considered individually, abnormal AFI was associated with an increased incidence of perinatal morbidity
- MBPP can be used as a method of antepartum fetal surveillance test to predict perinatal outcome and provide timely intervention in oligohydramnios pregnancies
- MBPP is a quicker and easier method for fetal antenatal surveillance
- In the presence of oligohydramnios, the occurrence of non-reactive NST, LSCS, meconium-stained liquor, fetal distress, low APGAR scores, low birth weight, and perinatal morbidity is high
- Determination of AFI can be used as an adjunct to other fetal surveillance methods. It helps to identify infants that are at risk of poor perinatal outcome.

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Original Article

A Study to Assess the Spectrum of Risk Factors and Clinical Features of Lacunar Strokes

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Abstract

Introduction: Lacunar strokes have a varied clinical presentation and etiological spectrum. Computed tomography and magnetic resonance imaging have greatly increased our ability of precise diagnosis. As the functional outcome of lacunar stroke is generally better than other types of strokes; therefore, this study was conducted to assess the risk factors and clinical presentation of lacunar strokes.

Materials and Methods: This cross-sectional, observational study was conducted on 40 patients aged above 45 years and having lacunar stroke patients. Relevant history and investigations were recorded.

Results: Mean age is 62.48 ± 8.76 years with male to female ratio of 2.63:1. Hypertension was present in 50% cases. HDL was deranged in 95% cases. Pure motor hemiparesis was present in 75% cases. Gangliocapsular area was involved in 29% cases.

Conclusion: Elderly males are most commonly affected. Hypertension and dyslipidemia are common risk factors. Pure motor hemiparesis is the most common presentation and gangliocapsular region is the most common site of lesion.

Key words: Gangliocapsular, Hemiparesis, Lacunar infarct, Lacunar stroke

INTRODUCTION

Historically, the term "lacune" has been used in medical field since long. It was first used to describe the small cavity that remains after a small stroke has healed.[1] Lacunar infarctions are small subcortical lesions with a size of less than 15 mm in diameter caused by occlusion of a penetrating artery from a large cerebral artery, most commonly from the Circle of Willis. These penetrating arteries arise at sharp angles from major vessels and are, thus, anatomically prone to constriction and occlusion.[2] Lacunar ischemic strokes comprise approximately 20% of all ischemic strokes. Many different types of lacunar stroke syndromes have been categorized.[3]

Historically, Dechambre, a French physician, first used the term "lacune" to describe a small cavity formed in the core of cerebral infarcts in the course of liquefaction and resorption of the infarct. Later, Max Durand-Fardel provided a more detailed description, identifying lacunae as healed, small infarcts.[4] He also coined the term "état criblé" which can be translated as "tissue riddled with holes" and "sieve-like state" and indicated "dilatations of perivascular space."[5]

Hypertension and diabetes mellitus are the major risk factors associated with lipohyalinosis and subsequent lacunar infarction. These risk factors are not present in all the cases and pathologically, the presence of small-vessel disease cannot be confirmed. Other postulated etiologies include atherosclerosis, embolism and stenosis, neurocysticercosis, infectious arteritis, and others.[6]

Historically, lacunar infarcts have been associated with a favorable short-term prognosis. However, over the years, it has been realized that lacunar infarcts are perhaps a more complex and less benign phenomenon than generally presumed. However, despite the availability of newer imaging modalities, particularly computed tomography (CT) scanning and magnetic resonance imaging, which have enabled the detection of most lacunae *in vivo*;[7] the research about lacunar strokes is still lacking.

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Since the functional outcome of lacunar stroke is generally better than other types of strokes, therefore, this study was conducted to assess the spectrum of risk factors and clinical presentation of lacunar strokes.

MATERIALS AND METHODS

This cross-sectional, observational, and analytical study was conducted after obtaining approval from the Institutional Ethics Committee. Patients aged more than 45 years and diagnosed with lacunar stroke in the medicine out-patient department (OPD) or admitted in the ward and who consented to participate were included in the study. Any patient having hemorrhagic stroke or acute stroke which appeared to be major cerebral infarct or strokes proven to be a space-occupying lesion or patients not consenting to participate in the study were excluded from the study. A total of 40 patients were included in the study.

Written informed consent was obtained from all the patients. Demographics, detailed medical history, including additional comorbidities and personal history, were recorded. The findings of laboratory and radiological investigations were recorded. Data were analyzed using appropriate software.

Statistical Analysis

All the data were analyzed using SPSS. Descriptive statistics were done. Results were expressed as mean ± standard deviation and proportions.

RESULTS

The mean age of the study population was 62.48 ± 8.76 years (range: 50–82 years). Males were more affected (72.5%) than females (27.5%). The distribution of risk factors in the study population is shown in Table 1.

Based on clinical diagnosis, pure motor hemiparesis was present in 75% of the cases, dysarthria and clumsy hand in 12.5% cases, transient ischemic attack (TIA) in 7.5% cases, and pure sensory hemiparesis and ataxic hemiparesis in 2.5% cases each.

The laboratory findings in the study population are described in Tables 2 and 3. 2D ECHO showed that 70% of the patients had normal findings, 25% had diastolic dysfunction, and 2.5% had lateral wall ischemia and MS each. About 92.5% of the patients had normal carotid Doppler, 5% had fibro-fatty plaque at RCCA, and 2.5% had fibro-calcific plaque and decreased intima-media thickness of bilateral CCA. CT showed that 30% of the cases had a single lesion while 70% of the cases had multiple lesions. According to the site of lesion, gangliocapsular area was involved in 29.0% cases, followed by corona radiata in 24.2% cases, thalamus in 22.5% cases, lentiform nucleus in 11.3% cases, and pons and internal capsule in 6.5% cases each.

DISCUSSION

In the present study, it was observed that most of the patients belong to the older age group with a mean age of study subjects was 62.48 ± 8.76 years. Similar were the findings in the study by Kaul *et al.*,[5] where the majority of the patients having lacunar infarct were between 55 and 75 years. Advancing age is an important risk factor for lacunar infarction as evident by previous studies by Kaul *et al.*[5] and Arboix.[8]

Furthermore, in the present study, a male preponderance was noted with male to female ratio of 2.63:1. This was similar to the study by Kaul *et al.*[5] where the ratio was 3.5:1.

Risk Factors

In the present study, it was found that smoking was the most common risk factor, present in 55% of the cases. Among the comorbidities, hypertension was the most common (50%), followed by diabetes (30%) and IHD (7.5%). Similarly, in the study by Horowitz *et al.*,[6] they found that hypertension was present in 68% of the cases followed by diabetes in 28% of the cases. Boiten and Ladder[9] also had noted similar findings.

In another study by Kaul *et al.*,[5] hypertension was more common (62%) than diabetes (38%). Smoking was also a

Table 1: Distribution of risk factors in the study population

Parameter	Number	Percentage
Smoking	22	55
Alcoholism	4	10
Diabetes mellitus	12	30
Hypertension	20	50
Ischemic heart disease	3	7.5
Others	5	12.5

Table 2: Distribution of laboratory findings in the study population

Parameter	Mean	SD	Range
Fasting blood sugar (in mg/dL)	134.43	49.22	66–295
Post prandial blood sugar (in mg/dL)	183.07	75.92	80–354
HBA1C (in %)	5.91	0.97	5–10.6
Total cholesterol (in mg/dL)	203.32	51.45	105–300
Triglycerides (in mg/dL)	158.53	67.04	66–413
LDL cholesterol (in mg/dL)	99.76	32.82	30–212
HDL cholesterol (in mg/dL)	32.65	11.09	20–94

Table 3: Distribution of laboratory findings according to the normal ranges in the study population

Parameter (cut off)	Normal		Abnormal	
	Number	Percentage	Number	Percentage
Fasting blood sugar (126 mg/dL)	25	62.50	15	37.50
Post-prandial blood sugar (200 mg/dL)	29	72.50	11	27.50
HBA1C (6.5%)	33	82.50	7	17.50
Total cholesterol (240 mg/dL)	33	82.50	7	17.50
Triglycerides (150 mg/dL)	21	52.50	19	47.50
LDL cholesterol (100 mg/dL)	27	67.50	13	32.50
HDL cholesterol (40–60 mg/dL)	2	5.00	38	95.00

significant risk factor in 28% of the cases. Similarly, Bejot *et al*.[10] observed that hypertension was the most common (69%), followed by diabetes (12.3%).

Clinical Features

In the present study, pure motor hemiparesis was the most common, followed by dysarthria and clumsy hand, TIA, pure sensory hemiparesis, and ataxic hemiparesis.

Kaul *et al*.[5] found that pure motor hemiparesis was the most common presenting syndrome in 45% patients. Ataxic hemiparesis and sensorimotor stroke accounted for 18% each and dysarthria-clumsy hand syndrome for 14%.

In another study, Arboix[8] found that pure motor hemiparesis was the most common syndrome (55%) followed by pure hemisensory stroke (18%).

Laboratory Findings

In the present study, dyslipidemia (especially HDL) was more common than hyperglycemia.

A study also observed that cholesterol levels were raised in 17% of the cases, triglycerides in 15.7% cases, LDL in 28.57% cases, and HDL was deranged in 61.4% of the cases. They also observed that HbA1c was deranged in 51.4% of the cases and FBS in 52.9% of the cases, similar to the present study.

Studies by Bots *et al*.[11] and Basharat *et al*.[12] noted that dyslipidemia, particularly with respect to HDL, was associated with an increased risk of all types of ischemic strokes.

Carotid Doppler

In the present study, most of the cases were normal (92.5%) with plaques present in only 7.5% of the cases.

Similarly, in the study by Horowitz *et al*.,[6] they identified atherosclerotic plaque as a possible embolic source in 23% of patients.

Site of Lesion

In the present study, gangliocapsular area was the most commonly involved area, followed by corona radiata, thalamus, lentiform nucleus, pons, and internal capsule.

Limitations

The study was limited by the OPD attendance of the patients having lacunar stroke. Therefore, the results may not be generalized.

CONCLUSION

It can be effectively concluded from the present study that lacunar stroke affects the elderly age group with male preponderance. Hypertension and dyslipidemia (particularly, HDL) are the commonest risk factors. Pure motor hemiparesis is the most common presentation and pure sensory and ataxic hemiparesis are the least common. Gangliocapsular region is the most common site of the lesion, while pons and internal capsule are the least commonly affected areas. Carotid Doppler is normal in the majority of the cases.

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Original Article

Study of Demographic Factors and Management Modalities of Post burn contracture Finger

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Abstract

Background: Burns constitute the second highest incidence of trauma-related deaths globally, second only to vehicular trauma both in developed and developing countries. Once a patient has been resuscitated, efforts are then made to improve wound healing to prevent scarring and contractures as contractures lead to a loss of function, poor cosmetic outcome, and reduced quality of life, pain, and psychological consequences. Contractures of the upper extremities may affect activities of daily living, such as grooming, dressing, eating, and bathing, as well as fine motor tasks. As burn survival rates have increased significantly in the past few decades, it is important to shift the focus on preventing and treating contractures.

Materials and Methods: This multicentric prospective comparative study was carried out on patients of the Department of Burns and Plastic Surgery, Civil Hospital and B. J. Medical College, Ahmedabad, and Sheth L. G. General Hospital, Ahmedabad, India, from December 2013 to December 2015. A total 51 adult subjects (both males and females) all the patients presenting to the outpatient department of both centers with post-burn contractures fingers or indoor patients developing contractures during their stay for the treatment of acute burns in the aforementioned time frame were included in the study. The data were collected with a pro forma regarding patient, defect, and treatment-related parameters. All the details of the patient that were relevant to the study were collected during the pre-operative, surgical, and post-operative periods and during follow-up which was later analyzed.

Results: Maximum number of the patients belonged to 21–30 years age group with almost equal sex preponderance. Most patients had flame burns (78%), 23 patients had total body surface area (TBSA) 10% or less, and mean TBSA was 13.43%. In total, 27 patients were neither advised physiotherapy nor splinting was done while 68.6% had a single finger contracture. Of total, 33.3% of patients presented between 1 and 2 years after burns. All patients belonged to either Grade 3 or Grade 4 contracture. Out of total, 64.2% of patients underwent contracture release with standard treatment guideline with very few complications of all modalities of treatment.

Conclusion: Female being involved in the activities such as cooking and outdoor work is mostly exposed to hazards of flame burns. Most of the patients were from rural setup, the lack of regular follow-up and subsequent absence of preventive measures can be attributed to the causative factor for contractures. Flame burns being deeper have more propensities for development of contractures. Length of stay, total burnt surface area, and lack of physiotherapy and splinting were found to be statistically important predictors for the presence of contractures. Rehabilitative strategies and preventive methods have not gained popularity despite widespread prevalence of post-burn contractures. Split-thickness grafting was the most common performed procedure followed by full-thickness grafting followed by local flaps. Most common complication in our series was wound infection and partial graft loss.

Key word: Contracture, Full-thickness skin grafts, Local flap, Post-burn contracture finger, Standard treatment guideline

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INTRODUCTION

Burns constitute the second highest incidence of trauma-related deaths globally, second only to vehicular trauma both in developed and developing countries.[1] The most common mechanisms of injuries are scald and flame burns, accounting for 45% and 20% of

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burn injuries, respectively. Flame burns usually result in an increased depth of burn. Chemical and electrical burns are less prevalent (<10%).[2] Once a patient has been resuscitated, efforts are then made to improve wound healing to prevent scarring and contractures as contractures lead to a loss of function, poor cosmetic outcome, and reduced quality of life (QOL), pain, and psychological consequences.[3,4] Contracture is abnormal deposition and maturation of collagen, which leads to hampering of function of joint or soft-tissue structure and cosmetic disfigurement or both. Contractures can be intrinsic or extrinsic. Intrinsic contractures result from injury or loss of tissue in the affected area, causing distortion and deformity of the part. Extrinsic contractures occur when tissue loss at a distance from an affected area creates tension that distorts the structure. Individuals with burn injuries are at risk for developing contractures due to multitude of factors. Patients with burns often are immobilized, both globally, as a result of critical illness in the severely burned, and focally, as a result of the burn itself because of pain, splinting, and positioning. Contractures interfere with skin and graft healing. Functionally, contractures of the lower extremities interfere with transfers, seating, and ambulation. Contractures of the upper extremities may affect activities of daily living, such as grooming, dressing, eating, and bathing, as well as fine motor tasks.[5,6] As burn survival rates have increased significantly in the past few decades, it is important to shift the focus on preventing and treating contractures.

MATERIALS AND METHODS

This multicentric prospective comparative study was carried out on patients of the Department of Burns and Plastic Surgery, Civil Hospital and B. J. Medical College, Ahmedabad, and Sheth L. G. General Hospital, Ahmedabad, India, from December 2013 to December 2015. A total of 51 adult subjects (both males and females) all the patients presenting to the outpatient department of both centers with post-burn contractures fingers or indoor patients developing contractures during their stay for the treatment of acute burns in the aforementioned time frame were included in the study.

Study Design

This was a prospective observational study.

Study Location

This was a tertiary care teaching hospital-based study done in the Department of Burns and Plastic Surgery, Civil Hospital and B. J. Medical College, Ahmedabad, and Sheth L. G. general hospital, Ahmedabad, Gujarat, India.

Study Duration

The study duration was from December 2013 to December 2015.

Sample Size

Fifty-one patients.

Inclusion Criteria

1. Patients with post-burn contracture of hand were included in the study.
2. Limitation in the range of motion in at least one plane of motion at a specified joint was considered to be a contracture at that joint.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients refusing for treatment.
2. Patients with contractures due to any other etiology other than burns.
3. Joint stiffness.
4. Acute infective condition.

Procedure Methodology

Collection of data

The data were collected with a pro forma regarding patient, post-burn contracture, and treatment-related parameters. All the details of the patient that was relevant to the study were collected during the pre-operative, surgical, and post-operative periods and during follow-up which was later analyzed.

Procedure

Both informed and written consent were taken about the procedure and the study on a preformed format. All the included patients were subjected to detailed history taking including demographic data (age, sex, and ethnicity) with special attention to length of hospital stay, length of intensive care unit stay, presence of concomitant medical problems (defined as medical problems that might alter the course of recovery from the burn, e.g., diabetes, chronic obstructive pulmonary disease, heart disease, and asthma), burn etiology, inhalation injury, neuropathy, amputation as the result of the burn injury, and total burnt surface area and total grafted area. A detailed general examination with importance to anemia and nutritional deficiencies was carried out. Local examination of contractures at all the joints was done and recorded. The joints of interest included the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints of finger. The subjects' active range of motion at each joint was measured using a goniometer with a standardized technique. Multiple planes of motion (i.e., flexion/extension) were investigated at each joint and the extent of functional and/or cosmetic impairment was recorded. A clinical photograph of the

contracture was then taken. Investigations with respect to preoperative fitness such as complete blood count, renal function tests, serum proteins, liver function tests, chest X-ray, and electrocardiogram whenever necessary were done in addition to local part X-ray. The classification of Sheridan and McCauley for the hand was modified for the current study involving all sites with contractures. This classification is useful for assessing function and physical management of contractures.

Patients with contractures belonging to Grade I and Grade II did not require surgery. They underwent manipulation under anesthesia and/or regular physical exercises at the physiotherapy department to regain full function. Patients with contractures in Grades III and IV of this modified classification had surgical release of their contractures. The defect was repaired using a technique appropriate for the site involved like incision or excision of contractures with skin grafting or local flaps. Postoperatively, patients were splinted using Plaster of Paris splints which were later replaced by thermoplastic splints and were started with physiotherapy within a span of 3 weeks to maximize function.

Follow-up procedure

Patients were followed up for 6 months following discharge and details pertaining to long-term complications, recurrence, and compliance with physiotherapy were noted. Patients discharged after September 2015 which followed up till February 2016.

Assessment of outcome

Statistical analysis was done using SPSS software (Statistical Package for the Social Sciences). Logistic regression model was used to find the predictors for the presence of contractures and various descriptive statistics were used to calculate frequencies, percentages, and means.

RESULTS

Demographic Factors

In our study, we studied 51 patients of post-burn contractures between the period of December 2013 and December 2015. Post-burn contractures were present in all age groups with the youngest patient being of 3 years while oldest was of 54 years. Maximum number of the patients belonged to 21–30 years age group (33.3%). Post-burn contractures were seen almost equally in or study with a slight preponderance toward the female gender. The mean distance from the treating hospital was 77.72 km.

Factors Related to Burn Injury

In our study of the 51 patients, most of the contractures were caused by flame burns (78%) while scald burns accounted for 5 (10%) patients and electric burns accounted for 6 (1 2%) cases. Of the 51 patients included in the study, 23 patients had total body surface area (TBSA) 10% or less while 14 patients had TBSA between 11 and 20%, 10 patients belonged to 21–30% while three patients had TBSA 31–40%, a single patient in 41–50%, and another single patient had more than 50% total burnt surface area. The mean TBSA was 13.43%. Of the 51 patients included in our study, 27 patients were neither advised physiotherapy nor splinting was done while 10 patients were given splinting and 8 patients were given only physiotherapy. Only six patients were advised both physiotherapy and splinting.

Factors Related to Contractures

Contracture frequency

Of the 51 patients, 35 patients (68.6%) had a single finger contracture, 11 patients had 2 finger contractures (21.6%), 3 patients had 3 fingers contractures (5.9%), and 2 patients had more than 3 fingers contractures (3.9%).

Duration between injury and time of presentation

Of the 51 patients included in the study, 9 patients presented within a year of burns while maximum (17 patients − 33.3%) presented between 1 and 2 years, those presenting between 2–3 years and 3–4 years were 12 and 5, respectively, and 8 patients presented after 4 years. The mean duration of presentation was 36.4 months.

Distribution according to classification

Of the 51 patients that were included in the study, 23 patients were in the Grade III of Sheridan and McCauley classification, that is, they had contractures which were functionally limiting with early changes in the normal architecture while 28 patients had Grade IV contractures, that is, there was loss of joint function with significant distortion of normal architecture. None of the patients belonged to Grades I and II.

Predictors of contracture formation

On subjecting the data of our study to statistical analysis for calculation of odds ratio and logistic regression with 95% confidence interval, it was found that of the parameters such as age, sex, length of stay total burnt surface area and absence of physiotherapy and splinting, length of stay ($P < 0.05$), total surface area burnt ($P < 0.05$), and lack of physiotherapy and splinting were statistically significant factors in predicting contracture formation.

Parameter	Odds ratio	*P* value
Age	0.976	0.018
Sex	0.722	0.056
Length of stay	1.056	0.000
TBSA burnt	1.032	0.003
Absent physiotherapy and splinting	1.044	0.000

Procedure	No. of procedures	Percentage
Split-thickness skin grafting	34	64.2
Full-thickness skin grafting	10	16.9
Local flap	07	3.8
Total	51	100.0

Out of the 51 patients in our study, wound infection and partial graft loss were among the most common complication which was seen in total two patients each, followed by flap tip necrosis in one patient and in follow-up of 6 months only one patient had recurrence of contracture which required reoperation. Out of 34 patients operated for contracture of finger with release + standard treatment guideline, one patient had wound infection, one patient had partial graft loss, and one patient had recurrence. Out of 10 patients operated for contracture of finger with release + full-thickness skin grafts (FTG), one patient had wound infection, and one had partial graft loss. Out of seven patients operated for contracture of finger with release and local flap, only one patient had tip necrosis of flap.

DISCUSSION

In our study, most patients were relatively young. This age group being the working class and involved in the activities like cooking is mostly exposed to hazards of flame burns. The socioeconomic implications of such disabling conditions are even more devastating given the economically productive age of the victims. Several published studies have described a similar frequent involvement of younger individuals. The incidence of burns and its sequel, the post-burn contractures are almost equal in both the genders. The female preponderance can be attributed to the fact that flame burns sustained during cooking due to unsafe modalities of cooking like *chulha*, kerosene stoves are still rampant in lower socioeconomic classes. Despite the advances in medical sciences and multiple initiatives taken by the government, there still remains a dearth of quality health care available at affordable prices in the periphery of major cities. The fact that an average patient had to travel for more than 70 km for the management of a functionally debilitating disorder exemplifies this fact. Furthermore, the lack of regular follow-up and subsequent absence of preventive measures can be attributed to long distances.

In a study carried out by Schneider *et al.*[7] for 985 patients, flame burns formed 61%, scald burns 7%, and electrical burns formed 9%. Flame burns by far are more common cause of burns as compared to scalds and electric burns. Flame burns are deeper and thus have more propensities for the development of contractures as compared to scald burns. In a study carried out by Schneider *et al.*,[7] burnt surface area (TBSA) was 25.1% while in Saaiq *et al.*,[8] the mean TBSA was 15.49% which was consistent with the result of our study with mean TBSA was 13.43%. In the study carried out by Saaiq *et al.*,[8] they have reported that none of the patients in their study had received splinting or physiotherapy. Despite widespread prevalence of the problem of post-rehabilitative strategies and preventive methods have not Illiteracy, poor health-care facilities, and lack of compliance on compounded the impact. In our study out of the 51 patients, 35 patients (68.6%) had a single finger contracture. Due to proximity of joints in the upper limb, particularly the hand and involvement of multiple joints in patients with higher total burnt surface area; multiple joints can be involved in contracture formation. In our study, maximum (17 patients − 33.3%) presented between 1 and 2 years. In a study carried out by Saaiq *et al.*,[8] the mean duration between injury and presentation was 4.6 years. Rural population, illiteracy, and lower socioeconomic status can be considered as the contributory factor for long duration between injury and presentation.

Maximum patients with contractures were from Class 3 (45.1%) and Class 4 (54.9%). Most of the patients belonged to the group where there was a loss of functional capacity, thus highlighting the fact that most of the patients do not seek treatment until there was disabling limitation of the joint movement and subsequent loss of earning capacity. On subjecting the data of our study to statistical analysis for calculation of odds ratio and logistic regression, the results of our study are in accordance with a similar study carried out by Schneider *et al.*[7]

Of the 51 patients in our study, split-thickness grafting was done in majority of patients (34 patients − 64.2%) while full-thickness grafts were done in 10 patients and flaps were done in seven patients. The usage of split-thickness skin grafts produces no major donor site morbidity. The operation time compared with the other treatment choices is shorter and the follow-up is easier. The post-operative hospitalization period is shorter. This probably explains the reason why split-thickness grafting was the most preferred treatment of choice. Thus, local flap treatment modality has better outcome with less chances of recurrence and coverage with FTG also has less chances of recurrence but partial graft loss is one of the known complications. In various studies carried out by authors such as Waymach, Cronin *et al.*, and Feldman[9,10] for the management of contractures for various joints, infection and recurrence remain as the major complication with rates ranging between 5 and 25% of cases. In a study carried out by Mody *et al.*,[11] the rate of recontracture was 13.6% while Cronin[9] has described a rate of 17% in his study.

CONCLUSION

The female preponderance can be attributed to the fact that flame burns sustained during cooking due to unsafe modalities of cooking. Most of the patients belonged to the age group of 21–30 years. This age group being involved in the activities like cooking and outdoor work is mostly exposed to hazards of flame burns. Most of the patients were from rural setup, the lack of regular follow-up and subsequent absence of preventive measures can be attributed to the causative factor for contractures. Thermal burns were the most common etiological factor. Flame burns being deeper have more propensities for the development of contractures. Hand deformities formed the major section of our study group which was followed by neck and axilla. Contractures have a disproportionate effect on the upper extremities. Length of stay, total burnt surface area, and lack of physiotherapy and splinting were found to be statistically important predictors for the presence of contractures. Most contractures belonged to Grade 4 of Sheridan and McCauley classification. Only 12% of patients had received physiotherapy and splinting after the initial burns. Rehabilitative strategies and preventive methods have not gained popularity despite widespread prevalence of post-burn contractures. Illiteracy, poor health-care facilities, and lack of compliance on patient's part have compounded the impact. Split-thickness grafting was the most common performed procedure followed by full-thickness grafting, followed by local flaps. Although chances of recurrence are least in full thickness grafting and local flap coverage procedure. Split-thickness grafting was the most common performed procedure followed by full-thickness grafting, followed by local flaps. Most common complication in our series was wound infection and partial graft loss, followed by partial flap necrosis and recurrence. Only one patient in our study suffered from recurrence in an operated case of post-burn contracture release with split-thickness skin grafting, which was treated with regrafting.

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Original Article

Post-operative Cerebrospinal Fluid Leak Following Transsphenoidal Pituitary Surgery: Predictive Factors and Management Options – A Single-Institute Experience

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Abstract

Background: Transsphenoidal route is the principal method for pituitary surgery with cerebrospinal fluid (CSF) leak most feared complication.

Materials and Methods: It is a retrospective analysis of 129 patients undergoing transsphenoidal surgery for pituitary tumors in the Neurosurgery Department of SMS Medical College, Jaipur (Rajasthan), from 2015 to 2018. The objectives were to determine (1) the incidence of CSF leak following transsphenoidal surgery; (2) demographic or intraoperative factors associated with postoperative leaks; and (3) techniques and efficacy of post-operative leak management.

Results: Post-operative CSF leaks occurred in 41.1% (53 of 129) of patients. Leaks were more common in males than females (52.83% vs. 47.1%) and in the age group of 21–40 years (54.72%). The incidence of post-operative CSF leaks was more in macroadenoma (84.9%) in comparison to microadenoma (13.2%). About 49.1% of patients with post-operative CSF leaks had tumors with suprasellar extension. Non-secretory, firm, and moderately vascular tumors were more frequently associated with post-operative CSF leaks. The presence of intraoperative leak was found to be a significant predictor of post-operative CSF leak. Out of 53 post-operative CSF leaks, 45 (84.9%) resolved with conservative measures and remaining six patients were cured with endoscopic reexploration.

Conclusions: CSF leaks following transsphenoidal surgery occurred in 41.1% of cases. The presence of macroadenoma with suprasellar extension on imaging and intraoperative leaks was independent predictors of post-operative leaks. Conservative management for manifested post-operative CSF leaks is a viable first-line option and those failing conservative measures can be tackled with endoscopic reexploration.

Key words: Cerebrospinal fluid leak, Endoscopic, Pituitary adenoma, Post-operative, Transsphenoidal

INTRODUCTION

Cerebrospinal fluid (CSF) leak is a recognized complication of transsphenoidal pituitary surgery. Incidence of post-operative CSF leaks ranges from 6% to 50% who underwent transsphenoidal operations; even higher rates have been reported after an extended transsphenoidal approach. However with newer techniques, the incidence has fallen to 1–10%.[1-4] Potential morbidities associated with post-operative CSF leaks include prolonged hospitalization, additional operations, meningitis, and tension pneumocephalus.[2] To avoid such complications, it would be helpful to identify patients at high risk for post-operative leak. Perhaps, these patients could be managed with more aggressive intraoperative or post-operative measures to prevent a CSF leak.

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Factors predictive of post-operative CSF leak remain poorly defined. Black *et al.*[5] reported a higher incidence of

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postoperative leak following resection of macroadenomas versus microadenomas (4.2% vs. 0.9%), whereas Seiler and Mariani[1] noted post-operative leaks to be more common when a visible CSF leak occurred during surgery versus the absence of an intraoperative leak (2.9% vs. 0.0%). Various materials and techniques for closure of the sella turcica have been described to prevent leaks or manage intraoperative leaks, but no studies have directly compared such strategies.

Management of the patients with post-operative CSF leak is controversial. Various strategies have been described, including non-operative management, CSF diversion, and reexploration.[5-7] A growing number of reports have demonstrated success with endoscopic techniques.[6,8,9] However, these reports describe CSF leaks of various origins and sites within the anterior cranial fossa. No study has specifically evaluated the efficacy of endoscopic management of sphenoid leaks following transsphenoidal surgery.

In the present study, we reviewed our experience with CSF leaks in the setting of transsphenoidal pituitary surgery. Various demographic and intraoperative factors were analyzed to elucidate any association with the occurrence of post-operative leaks. We also evaluated our strategies and results in managing post-operative leaks.

MATERIALS AND METHODS

The study was conducted in the Neurosurgery Department of SMS Medical College, Jaipur (Rajasthan). In total, 129 patients who had undergone transsphenoidal surgery for pituitary adenoma from 2015 to 2018 were enrolled in this retrospective observational study. All the necessary and relevant data were obtained from the medical records of patients which included admission sheets, pre-operative, operative and post-operative clinic notes, progress sheets, and discharge summaries. Data collected included patient age, sex, tumor size, extension, tumor characteristics (secretory or non-secretory, consistency, and vascularity), approach performed, intraoperative findings, method of sella turcica closure, and strategies used to manage post-operative CSF leak. Patients without complete documentation of the data were excluded from the study.

Statistical Analysis

Statistical analysis was performed with the MS Excel, SPSS, 23 version for Windows statistical software package (SPSS Inc., Chicago, IL, USA). The categorical data were presented as numbers (percent) and 95% confidence interval, to assess any significant association Chi-square test and odds ratio was used. Binary logistic regression analysis was done to find out significant independent indicators of post-operative leak probability. Multivariate analysis was performed using logistic regression analysis for dichotomous variables. $P < 0.05$ was considered statistically significant.

RESULTS

Between 2015 and 2018, 129 transsphenoidal surgeries were performed for pituitary adenoma. Out of 129 patients, 53 (41.1%) had post-operative CSF leak. There was no significant gender difference seen with respect to post-operative CSF leak; however, the incidence of post-operative CSF leak was significantly more in patients with age group in between 21 and 40 years [Table 1].

Incidence of CSF leaks was significantly higher in patients who had macroadenoma with suprasellar extension. Non-secretory, moderately vascular, and firm tumors had significantly higher post-operative CSF leak in comparison to other [Table 2]. There was no significant difference seen with different approaches (microscopic and endoscopic), extent of resection and the material used for reconstruction of sella [Table 3]. However, the incidence of post-operative CSF was much significant in patients who had intraoperative CSF leak in comparison to who did not. On multivariate logistic regression, age, tumor consistency, and intraoperative CSF leak were observed to be independent risk factors for post-operative CSF leak.

Table 1: Demographic profile of patients who have undergone transsphenoidal pituitary surgery between 2015 and 2018

Parameters	Total patients (*n*=129)		Post-operative leak present (*n*=53)		Post-operative leak absent (*n*=76)		Odds ratio (95% CI)	*P*-value
	*n**	%	*n**	%	*n**	%		
Age ≤20 years	8	6.2	2	3.77	6	7.88	0.667 (0.12–3.58)	9.94
Age 21–40 years	55	42.64	29	54.72	26	34.21	2.231 (1.05–4.65)	0.049
Age 41–60 years	66	51.16	22	41.51	44	57.89		
Male	81	62.79	28	52.83	53	69.74	2.057 (0.99–4.26)	0.077
Female	48	37.21	25	47.17	23	30.26		

*Number of patient out of total patients (*N*), % (*n*/*N*×100)

Table 2: Pituitary tumor characteristics

Parameters	Total patients (*n*=129)		Post-operative leak present (*n*=53)		Post-operative leak absent (*n*=76)		Odds ratio (95% CI)	*P*-value
	*n**	%	*n**	%	*n**	%		
Size								
Microadenoma	13	10.0	7	13.2	6	7.89	2.074 (0.675–6.375)	0.315
Macroadenoma	116	89.9	45	84.9	71	93	3.5 (1.220–10.044)	0.03
Extension								
Sellar	31	24.03	14	26.42	17	22.37	1.246 (0.552–2.814)	0.749
Suprasellar	68	52.71	26	49.1	42	55.26	0.406 (0.188–0.875)	0.033
Parasellar	30	23.26	13	24.53	17	22.37	1.128 (0.494–2.577)	0.941
Nature								
Secretory	61	47.29	20	37.73	41	53.94		
Non-secretory	68	52.71	34	64.15	34	44.73	2.211 1.075–4.545)	0.046
Recurrent	5	3.88	4	7.55	1	1.32	6.122 (90.664–56.412)	0.18
Consistency							Chi-square test (*P*-value)	
Hard	2	1.55	1	1.89	1	1.32	0.586	
Firm	90	69.77	31	58.49	59	77.63	0.034	
Soft	37	28.68	21	39.62	16	28.58		
Vascularity								
Mild	59	45.74	16	30.19	43	56.58		
Moderate	65	50.39	35	66.04	30	39.47	0.0005	
Severe	5	3.88	2	3.77	3	3.95	0.923	
Intraoperative CSF leaks	47	36.43	41	77.36	6	7.89	0.000	

*Number of patient out of total patients (*N*). % (*n*/*N*×100)

Table 3: Operative procedure and extent of resection

Parameters	Total patients (*n*=129)		Post-operative leak present (*n*=53)		Post-operative leak absent (*n*=76)		Chi-square test (p-value)
	*n**	%	*n**	%	*n**	%	
Microscopic	38	29.46	18	23.68	20	37.74	0.459
Endoscopic	91	70.54	35	46.05	56	61.5	
Extent of resection							
Complete	90	69.74	37	69.81	53	69.74	0.85
Partial	39	30.26	16	30.19	23	30.26	

*Number of patient out of total patients (*N*). % (*n*/*N*×100)

There were total 53 cases of post-operative CSF leak, mostly detected within 24 h of surgery and rest were within 5–7 post-operative days. Initially, all the cases were managed with head end elevation and oral acetazolamide. Out of 53 cases, CSF leak stopped in 12 (22.6%) patients within 12–24 h with this measure. Those who continued to have CSF leaks were put on CSF diversion using lumbar drain and with that CSF leaks resolved in 33 (62.3%) patients. Despite conservative measures, CSF leak failed to resolve in 6 (11.32%) patients. These patients were managed by endoscopic repair of the defect, following which all the CSF leak resolved [Table 4].

Out of 129 patients, only two patients developed meningitis and both were successfully managed with intravenous antibiotics. There was no incidence of pneumocephalus and intraoperative mortality. Two patients died in post-operative period due to medical complications.

Table 4: Management of post-operative CSF leaks

Treatment modality	Post-operative leak present *n**	Leak stopped	
		*n**	%
Head end elevation+Acetzolamide	53	12	22.6
Lumbar drain	41	33	80
Endoscopic repair	6	6	100

*Total number of patients

DISCUSSION

Our data suggest that certain factors can predict a greater likelihood of post-operative CSF leak in the setting of transsphenoidal pituitary surgery. Tumor characteristics and intraoperative CSF leaks were the two important factors that were associated with post-operative CSF leaks. In our study, patients between the age group of 21 and 40 years had significantly higher incidence of CSF leaks

in comparison to other age group but there was no sex predilection for CSF leak seen.

Tumor size was one of the important factors that have attracted researchers. Studies have reported a higher incidence of post-operative CSF leaks after resection of macroadenomas compared with microadenomas (3.8–4.2% vs. 0.9–1.3%).[5,10,11] Similarly, in our study, incidence of CSF leaks was more in macroadenomas with suprasellar extension. Most of these tumors were non-secretory in nature because of the late presentation in comparison to the secretory tumor which tends to become symptomatic in early phase due to hormonal factors.

Tumor consistency is also a factor that affects the rate of post-operative CSF leaks. CSF leaks were reported more commonly in firm tumors in comparison to soft tumors.[12,13] In our study, incidence of CSF leaks was more in firm tumor in comparison to soft tumor. One important noticeable thing is that the tumor texture was solely decided by the operating surgeon.

We found that patients with an intraoperative CSF leak had a significantly higher risk of post-operative leak. Intraoperative leaks occurred in 36% of our cases, well within the range of 18.1–53.2% reported in the literature.[1,10] The post-operative leak was seen in 53 (41.1%), out of which 77% had evidence of intraoperative leak while rest had no evidence of intraoperative leak.[1-4] This association was noted by Seiler and Mariani[1] who found post-operative leaks to be nearly 6 times as common when intraoperative leaks occurred. This finding suggests that patients with intraoperative CSF leaks may warrant more aggressive management to prevent post-operative leaks.

Several authors have described strategies for preventing CSF leak after transsphenoidal surgery,[1,2,5,14,15] many proposing more aggressive measures when an intraoperative leak occurs. Ciric *et al*.[2] described a technique of packing the sella with fascia, fat, and fibrin glue when an intraoperative leak is noted. In addition, a fragment of cartilage or bone is used to reconstruct the sellar floor. In our institute, reconstruction of sella was done with fat, fascia, and glue in 65.1% of cases while fat and fascia alone were used in 29.5% and in 6.2% cartilage were used.

There have been various strategies reported in the literature for the management of post-operative CSF leaks. Some authors have favored a trial of non-operative therapy involving lumbar drainage for 3 or more days.[5,6] However, Shiley *et al*.[16] have favored early reexploration without a trial of lumbar drainage. Laws *et al*. cited the ease and efficacy of reexploration as opposed to lumbar drainage, which may be unsuccessful or cause patient anxiety or both. There are no studies comparing the efficacy of non-operative therapy versus reexploration.[5,15]

In our studies, we had 53 cases of post-operative CSF leaks and the conservative approach was tried upfront in all the cases. The post-operative CSF leaks stopped in 45 (84.9%) patients with conservative measures. Out of 45 patients, 12 (22.6%) were managed with oral acetazolamide and head elevation; in the rest, 33 (80%) leaks were resolved with passive lumbar drainage. Our two patients died due to medical condition while they were on conservative measures. Out of total 53 patients, only 6 (11.3%) patients required endoscopic management.

Kelley *et al*.[6] reported successful endoscopic management of 7 out of 8 (87.5%) CSF leaks, most of which were secondary to transsphenoidal surgery. In our study, endoscopic management was successful in all the six patients with no operative or post-operative complication. The technique used by us for endoscopic management was similar to the studies reported in literature.[6,16,17]

CONCLUSIONS

CSF leaks following transsphenoidal surgery occurred in 41.1% of cases. The presence of macroadenoma with suprasellar extension on imaging and intraoperative leaks was independent predictors of post-operative leaks. Conservative management for manifested post-operative CSF leaks is a viable first-line option and those who fail to improve with conservative measures can be tackled with endoscopic reexploration.

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Original Article

Rapid Detection of *Mycobacterium tuberculosis* by Cartridge-based Nucleic Acid Amplification Test in a Rural Tertiary Care Hospital in Khanpur Kalan, Sonepat Haryana

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Abstract

Introduction: Tuberculosis (TB) is a major public health problem the infection affects up to one-third of the world population. Early diagnosis is needed for early patient management and successful patient treatment. The TB situation is worsened by the emergence and spread of multidrug resistant (MDR) TB cases. Mycobacterial culture is considered as the gold standard but is slow and usually takes 2–6 weeks' time to get the final result. Cartridge-based nucleic acid amplification test (CBNAAT) can detect TB along with rifampicin resistance in <2 h. This study was done to detect MDR TB by CBNAAT machine in a rural tertiary care hospital.

Materials and Methods: In the present study, samples presumptive of TB since February 2018 to July 2019 were subjected to CBNAAT for the diagnosis of rifampicin resistance.

Results: In the present study, total number of 3281 presumptive TB samples was tested by CBNAAT. Out of 3281 presumptive TB samples, 963 (29.35%) were *Mycobacterium* positive and rifampicin sensitive and 66 (2.01%) were positive for *Mycobacterium tuberculosis* and were rifampicin resistant. *Mycobacterium* was not detected in 2252 (68.64%) cases.

Conclusion: Detection of rifampicin resistant TB by CBNAAT is done within few hours. Consequently early diagnosis of TB patients helps in early and precise treatment and prevents transmission of MDR strains of TB in the community.

Key words: Cartridge-based nucleic acid amplification test, Multidrug resistant, Rifampicin, Tuberculosis

INTRODUCTION

Tuberculosis (TB) is a major public health problem the infection affects up to one-third of the world population, and almost 2 million people are killed by TB each year.[1] India is the highest TB burden country in the world. The global incidence of multidrug resistant (MDR) TB is 630,000 cases. India have one-tenth of the global burden with 64,000 cases.[2]

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Early diagnosis is needed for early patient management and successful patient treatment. The TB situation is worsened by the emergence and spread of MDR TB cases, defined as simultaneous resistance to at least rifampicin and isoniazid, with or without resistance to any other drug. False-negative results and misdiagnosis of TB suspects are common in developing nations, as most TB control programs use Ziehl-Neelsen smear microscopy, which has poor sensitivity and multiple visits are required that leads to higher default. Mycobacterial culture is considered as the gold standard but is slow and usually takes 2–6 weeks' time to get the final result and it requires proper infrastructure and technical expertise.[3]

In December 2010, WHO recommended use of a new Cartridge Based Nucleic Acid Amplification test

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(CB-NAAT), named GeneXpert system. The Xpert MTB/RIF assay employs five distinct molecular nucleic acid probes, each labeled with a differentially colored fluorophore and responding to a specific nucleic acid sequence within the rpoB gene of *Mycobacterium tuberculosis*. It can detect TB along with rifampicin resistance in <2 h.[4]

CBNAAT technique is not liable to cross-contamination; it requires minimal Biosafety facilities and has a high sensitivity in smear-negative pulmonary TB. The diagnosis of extrapulmonary TB (EPTB) is often difficult to establish, because number of bacteria in the specimens is often very low and collection often requires invasive procedures, and it is not easy to obtain multiple samples. GeneXpert is a useful tool for extrapulmonary specimens.[5]

This study was done to detect MDR TB by CBNAAT machine in a rural tertiary care hospital.

MATERIALS AND METHODS

Inclusion Criteria

Patients with clinical suspicion of pulmonary TB including symptoms of cough with or without expectoration for >2 weeks, weight loss, fatigue, hemoptysis, and loss of appetite were included in the study.

Exclusion Criteria

The following criteria were included in the study:

1. Samples received without clinical history.
2. Patient with history of lung malignancies or fungal infections.

This study was done at rural tertiary heath care hospital. The study was conducted in the department of microbiology for 1½ year. In the present study, samples presumptive of TB since February 2018 to July 2019 were subjected to CBNAAT for the diagnosis of TB and rifampicin resistant TB. Total of 3281 sputum samples of the patients with symptoms suggestive of pulmonary TB including both new cases and on treatment were received. All specimens were collected in pre-sterilized falcon tubes with three layer packing system, samples along with prescribed Performa containing details of patients such as name, address, age, and sex.

TB detection was done by Xpert MTB/RiF assay, made by Cepheid-Sunnyvale-USA. Sputum specimens were processed according to the GeneXpert Dx system operator manual given by Central TB division, Government of India, Guidance document for use of CB-NAAT under RNTCP. The assay is designed for extraction, amplification and identification of rpoB gene of *M. tuberculosis* as it accounts for more than 95% of mutations associated with rifampicin resistance, ensuring high degree of specificity by use of three specific primers and five unique molecular probes. The number of positive beacons, their detection timing indicated by rise of fluorescent signal above a predetermined baseline cycle threshold and the results of sample processing controls, allows the test to distinguish among the following results: No TB; TB detected, rifampicin resistance detected; TB detected, no rifampicin resistance detected; TB detected, rifampicin resistance indeterminate; and an invalid result. Xpert MTB/RIF cartridge is a disposable, single self-enclosed test unit in which all steps of NAAT, that is, sample processing, PCR amplification, and detection are automated and integrated. The manual steps involved in the assay are adding reagent to liquefy sputum and sample loading. The test procedure is made biosafe by tuberculocidal property of the assay's sample reagent.

RESULTS

This study was done at rural tertiary care hospital .The study was conducted in the department of microbiology for 1½ year. In the present study, samples presumptive of TB since February 2018 to July 2019 were subjected to CBNAAT for the diagnosis of TB and rifampicin resistant TB.

In the present study, total number of 3281 presumptive TB samples was tested by CBNAAT. In 3581 presumptive TB samples, *Mycobacterium* was not detected in 2252 (68.64%) cases. Out of 3281 presumptive TB samples, 963 (29.35%) were *Mycobacterium* positive and rifampicin sensitive [Figure 1]. Sixty-six (2.01%) were positive for *M. tuberculosis* and were rifampicin resistant.

DISCUSSION

In the present study, total number of 3281 presumptive TB samples was tested by CBNAAT. In 3581 presumptive TB samples, *Mycobacterium* was not detected in 2252 (68.64%) cases.

Out of 3281 presumptive TB samples, 963 (29.35%) were *Mycobacterium* positive and rifampicin sensitive. Sixty-six (2.01%) were positive for *M. tuberculosis* and were rifampicin resistant.

In the study done by Tripathi, *et al.* Status of drug resistance detected by CBNAAT, rifampicin sensitive TB was detected in 35.8%, and rifampicin resistant TB was in 53% samples by CBNAAT. In 10.7% cases, TB was not detected.[2]

In a study done by Agrawal *et al.* a total of 170 respiratory specimens (149 BAL and 21 Sputum samples) were tested. Among 170 samples, 42 samples (24.7%) were GeneXpert TB positive.[3]

In the study done by Arora *et al.* 84.21% samples were rifampicin sensitive and 15.78% samples were rifampicin resistant.[4]

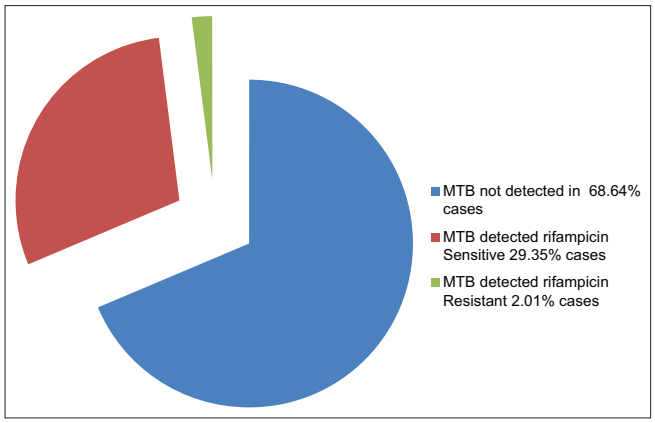

Figure 1: Detection of *Mycobacterium tuberculosis* by cartridge-based nucleic acid amplification test

According to RNTCP report 2018, in the year 2017 total 10,77,377 number of test were performed by 628 CBNAAT machines out of which 37,488 (3.48%) were rifampicin resistant TB.[6]

In the study done by Chikaonda *et al.* the Xpert MTB/RIF assay detected rifampicin resistance in 64/995 (6.4%) specimens.[7]

In a study done by Metcalfe *et al.* 28% samples were rifampicin sensitive and 20% samples were rifampicin resistant.[8]

In the study done by Iram *et al.* out of total 245 sample MTB was detected in 111 (45.3%) cases.[5]

In the study done by Sasikumar *et al.* the study enrolled 257 presumptive TB cases which included 132 pulmonary and 125 extrapulmonary presumptive TB cases Out of a total of 104 pulmonary TB cases, 73 were rifampicin-sensitive and 31 were rifampicin-resistant cases. 103 EPTB cases included 66 rifampicin-sensitive and 37 rifampicin-resistant cases.[9]

In the study done by Youngs *et al.* MTB was detected in 60 of 100 (60%) of CBNAATs and rpoB mutations that is rifampicin resistance was in 3 of 60 (5%) of MTB-D samples.[10]

In the study done by Sachdeva and Shrivastava samples subjected to CBNAAT, 58.3% were found to be positive for TB.[11]

In the study done by Chakraborty *et al.* in Pleural fluid samples CBNAAT were positive for MTB in (32%) subjects. Out of these patients, rifampicin resistance was detected in 8.3% individuals. In sputum, CBNAAT MTB was detected in 10.6% subjects. Among them, 12.5% had rifampicin resistance.[12]

CONCLUSION

Inability to rapidly diagnose and treat the affected patients leads to increased morbidity and mortality and development of secondary resistance and ongoing transmission of the disease. Diagnosis of drug resistance by conventional methods takes 6–8 weeks in detection. Detection of rifampicin resistant TB by CBNAAT is done within few hours. Consequently early diagnosis of TB patients helps in early and precise treatment and prevents transmission of MDR strains of TB in the community.

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Original Article

Oral Health Profile of Chronic Mentally Ill Patients in Moradabad City: A Cross-Sectional Study

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Abstract

Introduction: Good oral health is an important feature of good general health depression or chronic mental illness causes different types of oral problem such as xerostomia, acidic salivary pH, tooth decay, or periodontal disease. There is no study carried out in the Department of Psychiatry, Teerthanker Mahaveer Medical Hospital, Moradabad, which show oral health status of depression or chronic mentally ill patient.

Materials and Methods: The study was carried out in the out patient Department of Psychiatry, Teerthanker Mahaveer Medical Hospital Moradabad with total number of 250 patients.Type III method of examination was used. oral examination was done by the help of WHO oral health assessment form for adult 2013. Salivary PH was calculated by the help of universal PH indicator solvent.

Results: Mean score of decayed, missing, and filled tooth (DMFT) was 3.75 and the SD of DMFT is 1.75. Mean of salivary pH is 4.89 and the standard deviation (SD) is 0.81. Mean of periodontal pocket is 1.14 and the SD of periodontal pocket is 0.81. Mean distribution of pH in relation to periodontal pocket was 4.86 and the SD of 0.79 pH in relation to periodontal pocket was 0.79. By using ANOVA *P* value in relation to salivary pH and periodontal pocket was 0.23 which is less than 0.5 (i.e. significant) .

Conclusion: The adverse effect of antidepressants leads to xerostomia and salivary pH of psychiatry patient is more acidic so psychiatry patients are more periodontally compromise.

Key words: Antidepressants, Depression, Salivary PH

INTRODUCTION

Depression is a common mental health problem which involves low mood or loss of interest in daily activity. We can say that depression is a whole body sickness. Depression not only effects eating pattern, sleeping pattern and perspective of life and things the symptoms of depression can be seen from, weeks months or years.[1] There is difficulty in doing concentration and taking small decisions in life, unusual memory forgetfulness, negative thinking, feeling loss of interest, and feeling of sad in every small things, etc., these symptoms may get worst with the severity of depression.[2] People suffering from depression feels sad and losses their interest in everything. Their feeling of sadness and loss of interest lead to unemployment poverty housing insecurities and most important social isolation they completely detach themselves from society.[3,4] These factors play an important role in the poor oral condition. Good oral health is an important feature of good general health.[5,6] There is a two-way relationship between oral health and general health.[7] People suffering from depression or other mental disorder have very poor oral hygiene that leads to poor general health.[8] Depression patient or chronic mentally ill patient having poor oral hygiene experiences dental diseases such as dental caries erosion periodontitis.[7] People suffering from severe depression or other mental disease are more prone to dental disease because of their poor oral hygiene,[9] dental phobia,[10] dental treatment,[11] cost, or difficulty in getting dental facilities.[12] To cure depression, antidepressants (tricyclic antidepressants) are given.[13] These antidepressants show adverse side effect

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on orofacial region such as bruxism and xerostomia.[14] Xerostomia is also known as dry mouth or reduce in saliva flow. These drugs cause change in saliva flow and salivary concentration as well.[15-17] Saliva plays an important role in the maintenance of good oral health. Saliva helps in keeping oral cavity moist help in remineralization of teeth, protect our oral cavity from infections.[18] Saliva is the only oral tissue protective fluid and the importance of saliva only realize when the rate of flow of saliva is decrease.[19] Salivary flow is regulated by the autonomic receptors present salivary gland. Antidepressant blocks the effect of acetylcholine on the muscarinic receptors and leads to decrease in flow of saliva. If unstimulated saliva flow is under 0.7 ml/min, then it is consider as hyposalivation or xerostomia.[20] In hyposalivation or dry mouth condition, the patient experiences many problems such as problem in deglutition, difficulty in speaking, and highly prone to infections dental caries gingivitis periodontitis bruxism.[21] There is no clear mechanism by which antidepressant reduces saliva flow as in salivary gland, there are so many endogenous receptors (vasoactive intestinal peptide receptors) that regulate the flow of saliva.[22] Therapeutic drugs in the past decades play a huge in the treatment of depression or other mental disease but coin have its other side to as these drugs have orofacial adverse side effects. My research paper will highlight the adverse side effect antidepressants on unstimulated saliva, pH of saliva, and the buffing capacity is been evaluated moreover the side effect of antidepressant on oral cavity.

MATERIALS AND METHODS

A cross-sectional study was held in the outpatient department (OPD) of the Department of Psychiatry, Teerthanker Mahaveer Medical Hospital, Moradabad. The total sample size of study is 250 patients. A verbal guidance, nature of study was explained to the patient and informed written consent was obtained by the patient as per the Helsinki Declaration. The ethical clearance was obtained by the Ethical Committee of Teerthanker Mahaveer Dental College and Research Centre Ref No: TMDCRC/IEC/SS/19-20/PHD02.

Inclusion

- Both the sexes, males and female, and age group of 20–50 years were included in the study
- Patients with a history of systemic disease or condition that may affect the flow of saliva and composition of saliva
- Patient who are on antidepressant form past minimum 21 days.
- Patient who are on tricyclic antidepressants and selective serotonin reuptake inhibitors
- Patient who give a history of dry mouth.

Exclusion

- Patient with a history of any systemic disease that do not affect the flow of saliva
- Patient who are more than 50 years of age
- Patient who is having oral cancer or has undergone oral cancer surgery
- Patient who is under chemotherapy or radiation therapy
- Patient who has undergone oral prophylaxis in the past 6 months
- Patient who is suffering from Sjogren's syndrome or any other salivary gland disorders
- Patient who are not willing to fulfill the consent form
- Patient who are uncooperative.

Patients were examined according to type III examination (American Dental Association) which is used for public health survey.[23] Intraoral examination was done according to the World Health Organization (WHO) pro forma 2013.[24] The intraoral examination was done with the help of the WHO CPI probe. In the study periodontal status, dental caries is examined in each patient.

Saliva Sampling

The pH value of saliva of each patient is checked by the help of pH universal indicator solvent. "Common Minimal Technical Standards and Protocol" was the method by which saliva sample was collected. This technique was given by the WHO/International Agency for Research on Cancer guideline.[25] The patient was asked give there saliva sample in the morning with overnight fasting. The patient was asked not to eat or drink any liquid except water. After making patient comfortable, the patient was asked to wait for 5 min after 5 min the patient was asked to put their head in downward direction and ask to spit the saliva in a sterile tube the pH of saliva was checked by the universal indicator as soon as possible.

Statistical Analysis

The collected sample was entered into MS Excel (Window 2010). The statistical analysis was done in 21.0 version of Statistical Package for the Social Sciences. *P* value was calculated by the help of analysis of variance (ANOVA). $P < 0.05$ was considered statistically significant.

RESULTS

In the study, 250 were total sample size. The study was conducted in the OPD of Psychiatry, Teerthanker Mahaveer Medical Hospital, Moradabad. In the study, 63.2% (158) were male and 36.8% (92) were female. The mean age was 39.94 and the standard deviation (SD) of age is 11.61 [Table 1]. In the study, decayed, missing, and filled

tooth (DMFT) was also recorded in which 96% (241) of patients were having dental caries maximum no. of patients is suffering from tooth decay of decay which is 2.22 and the SD is 1.19. The mean 33.6% (74) of patients have missing tooth due to tooth decay mean of missing due to decay which is 0.82 and the SD is 1.39. About 29.2% (73) of patients having filled tooth. The mean if filled tooth is 0.52 and SD is 0.93. The mean of DMFT is 3.75 and the SD of DMFT is 1.75 [Table 2]. In the study, 72% (180) of the total study population have gingival bleeding is present, the mean of gingival bleeding is 0.72, and SD of gingival bleeding is 0.45. About 28% of the study population is not having gingival bleeding. About 40.4% (101) of the study population was having pocket of pocket depth of 6 mm or more. About 33.2% (83) of the study population was having pocket of pocket depth 4–5 mm. About 26.4% (66) of the study population was not having pocket. The mean of periodontal pocket is 1.14 and the SD of periodontal pocket is 0.81 [Table 3]. The loss of attachment of 4–5 mm was seen in 60.8% (152) of the study population. About 20.4% (51) was having loss of attachment of 6–8 mm. About 18.8% (47) of the study population was having loss of attachment of 0–3 mm.

Table 1: Distribution of DMFT, mean and SD of DMFT

Variables	Absent (%)	Present	Mean	SD
Decayed	3.6	96.4	2.22	1.19
Missing	66.4	33.6	0.82	1.39
Filled	70.8	29.2	0.52	0.93
DMFT	–		3.57	1.75

SD: Standard deviation; DMFT: Decayed, missing, and filled tooth

Table 2: Distribution of gingival bleeding and pocket score among the study subjects

Variables	*n*	%
Gingival bleeding present	180	72
Gingival bleeding absent	70	28
Pocket score 0	66	26.4
Pocket score 1	83	33.2
Pocket score 2	101	40.4

Table 3: Distribution of LOA score

Sextant	LOA score							
	0		1		2		X	
	n	%	*n*	%	*n*	%	*n*	%
16/17	52	20.8	118	47.2	80	32	0	0
11	137	54.8	113	45.2	0	0	0	0
26/27	37	14.8	124	49.6	52	20.8	37	14.8
36/37	87	34.8	142	56.8	21	8.4	0	0
31	111	44.4	139	55.6	0	0	0	0
46/47	47	18.8	152	60.8	51	20.4	0	0

The pH of saliva was record by the help of pH universal indicator solvent and the change in color of saliva was match by the pH guide, mean of salivary pH is 4.89, and the SD is 0.81 [Table 4]. In the study, 96% of the study population was having tooth decay, the mean distribution of pH in relation to decayed tooth was 4.77, and the SD of pH in relation to decayed tooth was 0.263. Using ANOVA $P = 0.65$ which was more than 0.5, so the relationship of pH with decayed tooth was not significant [Table 5]. In the study, 33.2% of the study population having periodontal pocket of depth 6 or more. Mean distribution of pH in relation to periodontal pocket was 4.86 and the SD of 0.79 pH in relation to periodontal pocket was 0.79. Using ANOVA $P = 0.23$ which is <0.5, so the PH in relation to periodontal pocket was significant.

DISCUSSION

Saliva is the liquid that help in keeping our oral cavity moist saliva is secreted from the major and the minor salivary gland present in the oral cavity, the secretion of the saliva from the salivary gland is monitored by the autonomic nervous system. However, there are many drugs like antidepressants that may alter the flow of saliva and affect the quantity and quality of flow of saliva. The effect of antidepressant is so intense, until the drug gets completely stable in plasma concentration.[25] In the study, the pH value of saliva of each patient is checked by the help of pH universal indicator solvent. "Common Minimal Technical Standards and Protocol" was the method by which saliva sample was collected. This technique was given by WHO/International Agency for Research on Cancer guideline.[25,26] The patient was asked give there saliva sample in the morning between

Table 4: Mean distribution of pH in relation to decayed tooth

Decayed teeth	Mean	SD
Present	4.77	0.263
Absent	4.90	0.820
ANOVA test	0.207	
P-value	0.65	

ANOVA: Analysis of variance; SD: Standard deviation

Table 5: Mean distribution of pH in relation to periodontal pocket

Periodontal pocket	Mean	SD
Present	4.86	0.79
Absent	5	0.84
ANOVA test	1.4	
P-value	0.23	

ANOVA: Analysis of variance; SD: Standard deviation

9:00 am and 11:00 am with overnight fasting. The patient was asked not to eat or drink any liquid except water. After making patient comfortable, the patient was asked to rinse mouth by water, the patient was asked to wait for 5 min after rinsing the oral cavity after 5 min, the patient was asked to put their head in downward direction and ask to spit the saliva in a sterile tube, the pH of saliva was checked by the universal indicator as soon as possible. Analysis salivary pH was measured with the help of pH universal indicator, solvent salivary pH was analyzed with the pH guide. The normal pH range of saliva is 6.2–7.6. In the study, mean of salivary pH was 4.89 and the SD was 0.81; in the study, 96% (241) of patients were having dental caries maximum no. of patients is suffering from tooth decay of decay is 2.22 and the SD is 1.19. Mean distribution of pH in relation to decayed tooth was 4.77 and the SD of pH in relation to decayed tooth was 0.263. Using ANOVA $P = 0.65$ which was more than 0.5, so the relationship of pH with decayed tooth was not significant.

In the study, 40.4% (101) of the study population was having pocket of pocket depth of 6 mm or more. Mean of periodontal pocket is 1.14 and the SD of periodontal pocket is 0.81. Mean distribution of pH in relation to periodontal pocket was 4.86 and the SD of 0.79 pH in relation to periodontal pocket was 0.79. Using ANOVA $P = 0.23$ which is <0.5, so the pH in relation to periodontal pocket was significant.

Kebede *et al.* (2011) conducted a study on psychiatric disorder patient in which he found out the mean DMFT score of psychiatric patients was 1.9462.12 (mean 6SD). Along with this, 24% of the psychiatric patients had a healthy CPI score. They also documented that incorrect tooth brushing technique and sweet intake are also associated with dental caries and found that the oral health status of the psychiatric patients was poor.

Zaclikevis *et al.*, 2009; Rinaldi *et al.*, 2015; and Mattioli *et al.*, 2016, conducted a study in which he found that antidepressant (lorazepam) shows some changes in the parotid gland of the rats there was reduction in the flow of saliva and apoptosis was also seen in the salivary gland.

CONCLUSION

Depression is a whole body disease. Oral health and general health have two-way relationship. To cure depression, antidepressants are given which lead to xerostomia due to decrease flow of saliva in mental patient lead to many other dental problems. Oral health education is must for psychiatric patients as their salivary PH is comparatively low and should be asked to follow proper oral hygiene aids as well as routine dental visits.

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Original Article

Clinical Profile of Neem Oil Encephalopathy in Children

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Abstract

Background: Neem oil commonly used as native medicine can cause toxic encephalopathy.

Objective: The objective of the study was to study the clinical and epidemiological features of children with neem oil poisoning.

Materials and Methods: This was a retrospective analysis of case records.

Results: Among the 88 cases, the mortality was 30.68%. In survived patients are cortical blindness (5.7%) and recurrent convulsion (2.3%), no sequelae were found in 61.4%.

Conclusion: Convulsion is the most common presentation of neem oil poisoning. Death is usually associated with prolonged convulsion and is usually within first 48 h.

Key words: Children, Encephalopathy, Neem oil, Status epilepticus

INTRODUCTION

Neem oil is used as a traditional medicine in South India for treatment of various ailments such as cough, cold, and diarrhea. Consumption of neem oil can, however, result in varied toxic systemic and neurological manifestations.[1] Neem oil is a vegetable oil pressed from the fruits and seeds of Neem (*Azadirachta indica*), an evergreen tree which is endemic to the Indian sub-continent. Neem oil is generally light to dark brown, bitter and has a rather strong odor that is said to combine the odors of peanut and garlic. It comprises mainly triglycerides and large amounts of triterpenoid compounds, which are responsible for the bitter taste. Neem oil also contains steroids (campesterol, beta-sitosterol, and stigmasterol) and a plethora of triterpenoids of which Azadirachtin[2] is the most well-known and studied. The Azadirachtin content of neem oil varies from 300 ppm to over 2000 ppm depending on the quality of the neem seeds crushed.

The socio cultural practices involved in child rearing, mostly irrational cause a great impact in childhood morbidity and mortality. One such harmful practice is the instillation of vegetable oil (usually gingili oil) in the child's nose and mouth as a cure for respiratory infections. This is a widespread custom in rural Tamil Nadu. Healthy children probably having a viral respiratory illness when subjected to this practice eventually develop more serious complications. When neem oil is used for the same custom, children present with encephalopathy and seizures.[1]

Aim of the Study

The aim of the study was to study the clinical and epidemiological features of children with neem oil poisoning.

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MATERIALS AND METHODS

Study Centre

The study was conducted in a tertiary care center in South Tamil Nadu.

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Study Design

It is a retrospective descriptive study for 3 years by analyzing the case records.

Inclusion Criteria

All cases with history of neem oil ingestion and developing features of encephalopathy and other toxic features were included in the study.

Exclusion Criteria

Other known cause for convulsion such as neuroinfection and neurodegenerative disorder was excluded from the study.

Methodology

All children with history of neem oil ingestion were enrolled in the study as per the criteria specified. Following a brief history and rapid evaluation, the children were resuscitated and managed as per the designed protocol. Blood samples for the biochemical estimation of glucose, urea, creatinine, and bicarbonate were collected, as soon as an intravenous access was first established for management. Supportive therapy, such as inotropes and mechanical ventilation were provided, as and when required. The status epilepticus is managed as per the standard protocol used in our institution.

Analysis

Data will be entered in excel spread sheet and analyzed using simple descriptive statistics.

RESULTS

Total number of cases admitted with neem oil encephalopathy was 88. Among these 27 children succumbed to the illness. The mortality rate is 30.68%. Male:female ratio is 1.05:1. Age ranges from 36 days to 7 years mean value 1.193 standard error of mean 1.19 standard deviation 1.42 Q1 .25 Q3 1.5. Age-specific mortality rate ranges 1 month –1 year 26.67%; 1–2 years 30.77%; 2–3 years 66.67%; 3–4 years 25%; and 4–8 years 40%. The places distribution is as follows Madurai urban 21 (23.86%), rural 43 (48.86%), and neighboring districts 24 (27.3%). Patients presented with convulsion (73.3%), postictal state (22.19%), shock (3.1%), respiratory distress (1.5%), and route of administration-oral (100%). The amount of neem oil given ranges from 1 ml to 7.5 ml the mean value 3.99 standard error of mean 0.14 standard deviation 1.36 Q1 3 Q3 5. Patients were administrated neem oil for abdominal pain (34.1%), respiratory infection (29.5%), deworming (23.9%), unknown reason (6.8%), and convulsion (2.3%). The onset of convulsion ranges from 30 min to 5 h the mean value 2.1 standard error of mean 0.11 standard deviation 1.02 Q1 1.31 Q3 2.5. The total duration of convulsion ranges from 0.17 h to 8.3 h the mean value 2.56 standard error of mean 0.22 standard deviation 2.08 Q1 1 Q3 4.

The total duration of hospital stay [Table 1] ranges from 50 min to 21 days the mean value 4.3 days standard error of mean 0.38 standard deviation 3.58 Q1 2 Q3 6. The complication while undergoing treatment is as follows: Need of ventilatory support (6.8%), need of inotropic support (8.0%), need of ventilatory and inotropic support (4.5%), aspiration (2.3%), shock (0.2%), and no specific complication (78.4%). The sequelae [Figure 1] in survived patients are cortical blindness (5.7%), movement disorder and recurrent convulsion (2.3%) no sequelae was found in (61.4%) .The laboratory values was normal in (84.1%), low glucose was presented (5.7%), elevated urea creatinine (4.5%), elevated AST ALT (2.3%), and low bicarbonate (3.4%). EEG revealed background abnormalities in the form of diffuse slowing with paroxysmal abnormalities in the form of spikes and wave discharge in 85% (49 of 57). CT scan revealed diffuse cerebral edema in 36 (of 42). CSF analysis, done in ten patients, was normal. Autopsy done in 27 cases showed following findings-diffuse cerebral edema, brain is congested more over parieto-occipital area and petechiae hemorrhages seen. No significant changes are seen in liver and lung except mild congestion. However, these changes are nonspecific and can occur in any hypoxic

Table 1: Hospital stay and outcome

	Survived	Expired	Total
0–2 Days	9	23	32
2–5 Days	28	4	32
>5 Days	24	0	24
Total	61	27	88

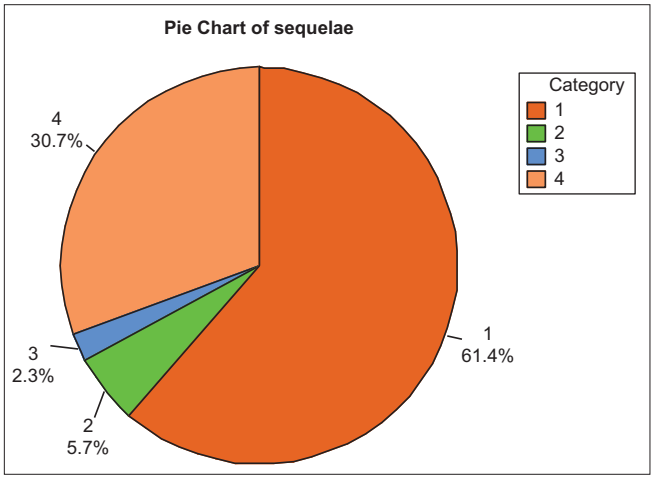

Figure 1: Sequelae. (1) Recovered without sequelae, (2) Cortical blindness, (3) Movement disorder and recurrent convulsion, (4) Expired

encephalopathy. There is no relation between gender and mortality, male expired 12 (26.66%) and female expired 15 (34.88%); $P = 0.102$ (insignificant). Duration of convulsion correlates with mortality [Table 2], but it is not statistically significant $P = 0.115$.

DISCUSSION

The incidence was decreased markedly in the 3rd year. However, this may be a transient phenomenon .In a study conducted by Lai *et al.*,[3] two children with neem oil poisoning were reported that the metabolic acidosis was not present in the present study. CSF analysis was normal as in the study and both children were recovered. In a study conducted by Sinniah *et al.*[4] most of the cases between the age group of 21 days and 4 years which is similar to this study. However, there is no recurrent vomiting and Reye syndrome was not found in this study. The mortality was 15% compare to 30.68% in this study. Eight (62%) required assisted ventilation as compare to in this study. The onset of convulsion is 30 min to 4.5 h as compare to in this study. In a study conducted in JIPMER should eight out of 218 cases were the cause of coma and the mortality was 48%. In the study by Sinnaiah *et al.* was showed that the extracted neem seed oil is toxic at least in children.

Child recovering from neem oil encephalopathy had only transient cortical blindness which recovered over 1–3 months. The severity varies from asymptomatic to death and it is probably genetic makeup of the child versus concentration of neem oil. The children are more prone for toxicity than adults, probably, and mechanism for control of seizure activity are fragile in younger children and may get disrupted with minimal abnormalities in neurofunction. Similarly, Kroczka *et al.*[5] report that SE appeared more frequently in children diagnosed with epilepsy during the first 2 years of life.

Prasad *et al.*[6] comments that longer a seizure lasts, the more difficult it becomes to control and that seizures can have immediate and long-term adverse consequences on immature and developing brain. The neem oil encephalopathy, unique to our area may be responsible for this slightly higher mortality.

Table 2: Duration of convulsion and outcome

	Survived	Expired	Total
0–2 h	44	5	49
2–4 h	14	10	24
>4 h	3	12	15
Total	61	27	88

Sagduyu *et al.*[7] report a lower case fatality rate of 21% in status epilepticus. However, the mortality rate reported in text books is around 5% in status epilepticus. Meta-analysis by Gilbert *et al.*[8] states that outcomes in India could be different for non-drug related or etiology related reasons. For example, slow transportation to the site of medical care could both increase mortality and decrease efficacy. Differences in intensive care unit practices also could alter mortality. Kroczka *et al.* add that the low frequency of SE in their study can be related to continuous access to pediatric neurologist and experienced nurse team.

CONCLUSIONS

1. Convulsion is the most common presentation of neem oil poisoning.
2. Death is usually associated with prolonged convulsion and is usually within first 48 h.
3. Neem oil encephalopathy has high mortality compared to other causes of status epilepticus.
4. Reye syndrome is not detected in this study.

Limitations

1. EEG could not be done in all cases and EEG monitoring of therapy of refractory SE was not done due to limited resources and lack of bedside EEG monitor.
2. CT brain was not done in some children due to the poor general condition of the patient, preventing transport to the CT-scan room.
3. Method of extraction of neem oil could not be elicited due to practical difficulties. Laboratory estimation of serum ammonia was not done.
4. Laboratory estimation of serum ammonia was not done.

Recommendations

1. Public awareness program should be initiated regarding neem toxicity in children especially in high-risk area.
2. Toxicological studies on neem oil should be made available in Regional forensic laboratory.
3. Large scale community based and (animal) experimental studies on neem oil is essential as it has socio-cultural background.

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Original Article

Association of Hemoglobin-A1c with Healing in Diabetic Cutaneous Wound – A Prospective Study

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Abstract

Background: Glycosylated hemoglobin is widely used as a measure for glycemic control in patients. Only very few studies in the literature states that hemoglobin A1c (HbA1c), which is a standard measure of glycemia over 2–3 months, is related to wound-healing rate. Our objective was to identify the common variables most strongly related to wound healing rate in a hospital-based population of individuals with diabetes. We hypothesized that among common laboratory tests, clinical and demographic variables, higher HbA1c values would be the most associated with decreased daily wound-healing rate.

Objective: The objective of the study was to establish the association of HbA1c with healing in diabetic cutaneous wounds.

Methodology: A prospective study in patients who were admitted to the general surgery department for the treatment of diabetic cutaneous wounds at MOSC Medical College was evaluated (from September 2011 to August 2013). Wounds in them were measured using calibrated measuring tape at the time of admission and same procedure repeated at the time of discharge and at follow-up; thereby wound healing rates were measured. A semi-structured questionnaire was also filled while interviewing the patients at the time of admission. Collected data were entered in Excel and analyzed using SPSS version 16. Among all variables analyzed, only HbA1c was significantly associated with wound area healing rate. A change in wound area per day showed for each 1.0% point increase in HbA1c, the wound-area healing rate per day decreased by 0.219 cm^2 (95% confidence interval): –0.290, –0.148, $P = 0.0001$). A sensitivity analysis done stratified by peripheral arterial disease status and neuropathy status showed an improvement in statistical significance.

Conclusion: Hba1c is an important clinical predictor of wound healing rate and the relationship holds stronger particularly in neuropathic wounds and in peripheral arterial diseases.

Key words: Glycosylated hemoglobin, Neuropathy, Peripheral arterial disease

INTRODUCTION

Diabetes mellitus is a metabolic disorder caused by either a lack of insulin, or resistance to its effects, or both. In 2004, an estimated 3.4 million people died from consequences of high fasting blood sugar.[1] Poor glycemic control and presence of diabetic complications are commonly regarded as risk factors for mortality and morbidity.

Diabetic foot infections are one of the major long-term complications of type 2 DM which can result in gangrene and lower extremity amputation.

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Diagnostic criteria for DM

1. Fasting plasma glucose ≥7 mmol/L (≥126 mg/dl)
2. 2 h PPBS after ingestion of 75g of oral glucose load (OGTT) ≥11 mmol/L (≥200 mg/dl)
3. Hemoglobin A1c (HbA1c) result >6.5%.

Any two out of three criteria or 1 plus symptoms of DM are diagnostic.

Around 1977, the HbA1c was first introduced to clinical laboratories for diabetes monitoring. At the present time, the HbA1c is used worldwide as the marker of long term glycemic control and also a therapeutic target in the prevention and delay of the development of hyperglycemic complications.[2-4]

Over 100 known physiological factors contribute to wound healing deficiencies in individuals with diabetes. These include decreased or impaired growth factor production,[5-7]

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angiogenic response[7,8] macrophage function[9] collagen accumulation, epidermal barrier function, quantity of granulation tissue[7] keratinocyte and fibroblast migration and proliferation, number of epidermal nerves[10] bone healing, and balance between the accumulation of ECM components and their remodeling by MMPS.[11] The wound healing process consists of four highly integrated and overlapping phases: Hemostasis, inflammation, proliferation, and tissue remodeling or resolution.[12] These phases and their bio-physiological functions must occur in the proper sequence, at a specific time, and continue for a specific duration at an optimal intensity.[13] Wounds that exhibit impaired healing, including delayed acute wounds and chronic wounds, generally have failed to progress through the normal stages of healing, such wounds frequently enter a state of pathological inflammation due to a postponed, incomplete, or uncoordinated healing process. Most chronic wounds are ulcers that are associated with ischemia, diabetes mellitus, venous stasis disease, or pressure damage.

The HbA1c level is proportional to average blood glucose concentration over the previous 4 weeks to 3 months. Poor glycemic control is associated with the presence of neuropathy and increased risk for wounds and amputations. Foot problems most often develop when there is neuropathy, poor vascularity, or changes in the shape of toes. In the setting of Kerala, where the study was done, also there is a significant dearth of information regarding association of HbA1c to wound healing.

METHODOLOGY

Materials and Methods

This prospective clinical study was done to identify the common variables most strongly related to wound healing rate in a population of individuals with diabetes admitted in a tertiary care center in the state of Kerala, India. We hypothesized that among common laboratory tests, clinical and demographic variables, and higher HbA1c values would be the most associated with decreased daily wound healing rate.

A total of 101 patients who are diabetic for more than 5 years, with peripheral cutaneous wounds from OP departments and general wards of department of general surgery and plastic surgery between September 2011 and August 2013 were selected for our study as sample group.

Exclusion Criteria

The following criteria are excluded from the study:

1. Seriously ill patients admitted in ICU with multiple comorbidities
2. Diabetic wounds with osteomyelitis (Wagner's classification three and above)
3. Duration of diabetes less than 5 years
4. Patients who are having multiple immunocompromised states. (Tuberculosis, AIDS, severe renal disease, and chronic liver disease).

Wagner's wound classification system:

1. No open lesions, may have deformities or cellulitis
2. Superficial ulcer
3. Deep ulcer to tendon or joint capsule
4. Deep ulcer with abscess, osteomyelitis, or joint sepsis
5. Local gangrene – forefoot or heel
6. Gangrene of entire foot.

Wounds were measured using calibrated measuring tape at the time of admission and same procedure repeated at the time of discharge and after 1 month for follow-up; thereby wound healing rates were measured. The area of wound and the largest width and largest length were traced to obtain wound dimensions. A semi-structured questionnaire was also filled while interviewing the patients for complete information on baseline demographic and clinical variables. Collected data were entered into Excel and analyzed using SPSS version 16. Clinical information collected included vital signs (BP, PR, and temperature), status of neuropathy (Semmer Weinstein filament – Medical Monofilament manufacturing LLC, Plymouth, MA), and peripheral arterial disease status (palpatory and ABPI measurement using a hand held Doppler).

All wound treatments were documented and found to be homogeneous for all patients with diabetic wounds. Standard treatment for diabetic wounds includes removal of non-viable tissue, local dressing (antimicrobial dressings with silver), control of blood glucose levels, offloading with proper shoes if the wound is on the lower extremity and antibiotic treatment if infection is present.

Laboratory test results (HbA1c, Hb, ESR, Platelet count, blood sugars, and white blood cell count) and BMI, smoking status, and alcoholic history data were included in the study.

The change in wound area in cm^2 per day was the outcome for our primary analysis. The change in wound area per day was calculated as the difference between wound area at visit 1 (baseline) and at a subsequent visit divided by the number of days between the two visits (median of 32 days, interquartile range: 18–61). We estimated the change in wound area (cm^2 per day) using a multiple linear regression model with robust SE and adjusted for clustering of wounds within individuals. Model discrimination was assessed with the use of Akaike's Information Criterion values. HbA1c

was expressed per 1% point, for clinical interpretability. Inferences were the same when we log transformed HbA1c to make the variable more normally distributed, so HbA1c was left untransformed for clinical interpretability. Variables of interest included age, gender, pulse, systolic and diastolic blood pressures, body mass index, HbA1c, peripheral neuropathy, peripheral artery disease, smoking, alcoholism, hemoglobin, ESR, RBS wound number, wound location, and white blood cell count. We tested for trends across the medians of HbA1c categories. To assess the possibility of differential healing rates between neuropathic foot wounds, and other wounds in diabetic patients (mainly large surgical non-healing wounds), we performed a sensitivity analysis stratified by wound on weight-bearing portions of the foot in individuals with documented peripheral neuropathy. In addition, we performed a sensitivity analysis stratified by peripheral artery disease status. All reported P-values are two-sided and $P < 0.001$ was considered statistically significant. Analyses were performed using SPSS version 16.

The study was approved by the institutional ethics committee of the hospital.

RESULTS

The demographic and clinical characteristics of the 101 individuals at the time of admission were shown both overall and stratified by HbA1c categories in Table 1. In the entire sample group, the mean age was 59 years, mean HbA1c was 8.6 gm%. Age distribution against Hba1c categories is shown in Figure1.

The mean base line area was 4.872 cm^2, and the mean change in area per day was 0.081 cm^2 per day. Despite being the smallest size (3.902 ± 0.198 cm^2) at baseline, wounds at the highest level of HbA1c (>8 gm%) healed at the slowest rate (0.036 ± 0.002 cm^2 per day). Conversely, ulcers with larger baseline size in the lowest(<7 gm%)(5.305 ± 0.387cm^2) and intermediate(7-8 gm%)(5.783 ± 0.388 cm^2) HbA1c categories both had greater healing rates than did those with smaller baseline size in the highest HbA1c category. Although there trended to be an inverse association between baseline wound size and healing rate, statistical significance was not reached after adjusting for HbA1c and other variables in our model ($P = 0.213$). Association of Hba1c with wound area healing rate (log CAREA) in diabetic cutaneous wounds is shown in Figure 2. Depiction of wound healing pattern in two diabetic individuals is shown in Figure 3. Figure 4 is a Scatter plot depicting a negative correlation of HbA1c and change in wound area per day (log CAREA) and Figure 5 is error plotting showing significance of log CAREA against HbA1c group.

51.5% of our entire study group comes from an urban background, we observed a significant increase (43%) [Table 2] in subjects from rural community who are having their hba1c >8 gm%.

The HbA1c values among different occupations (skilled workers, unskilled workers, unemployed) is explained in Table 3. 45.5% of our entire study group comprised of unskilled unemployed subjects, and in that group around 60% had an HbA1c value >8 gm%.

62.4% of our study group were having smoking addiction in the past (had smoked cigarette/bidis for more than 10 years) of which 28% of the subjects are current smokers. Even though we got an inverse correlation while plotting adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and current smoking status a statistical significant relation was not obtained ($P = 0.859$) [Table 4].

Table 5 shows 60% of our study group having alcoholism as addiction of which 23.8% were frequent alcoholics.

Table 1: Clinical characteristics of all participants at the time of admission stratified by HbA1c

Patient variable	HBA1C group						Total	
	≤7		7–8		>8			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Age	55.667	2.250	61.174	2.025	61.385	1.317	59.13	1.131
BMI	26.406	0.125	27.001	0.155	27.292	0.128	26.88366	.086300
HBA1C	6.849	0.033	7.791	0.059	10.923	0.115	8.637	.1909
SYSTBP	129.641	1.434	139.261	5.842	145.744	1.605	138.05	1.701
DIABP	73.692	0.803	80.087	0.800	82.256	1.034	78.46	.658
PULSE	73.872	0.394	75.130	0.791	78.846	0.810	76.08	.448
WBC	8383.974	227.656	8213.913	470.224	8786.769	196.103	8500.78	157.737
Hb	11.874	0.175	11.178	0.239	11.372	0.145	11.522	.1063
ESR	6.051	0.913	7.261	1.421	5.923	0.752	6.28	.556
PLATC	2.500	0.078	2.719	0.144	2.425	0.082	2.5210	.05520
WOUNDNO	2.128	0.098	2.304	0.183	2.385	0.108	2.27	.070
RBS	155.842	5.824	232.391	7.897	174.974	7.969	180.91	5.120

Adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and current frequent alcoholic status didn't show a statistical significant association ($P = 0.24$).

The most common location for wounds in our study population was the lower extremity, with 42% of wounds occurring on the leg or ankle and 42.5% of wounds occurring on the foot. The remainder of the wounds occurred on the buttocks (5.5%), the abdomen or chest (3%), the arms(3.5%), the groin (3.0%), and the back (0.5%) [Figure 6].

69% of the total individuals were males, and majority of the patients belong to Christian and muslim community.

There was a mean of 2.3 wounds per individual (232 wounds in total). We divided the wounds into two broad categories of foot wounds with documented neuropathy ($n = 155$) that are classic diabetic wounds versus chronic wounds elsewhere ($n = 77$), which are predominately surgical wounds that have failed to heal. Participants who are having neuropathy and those who are not having neuropathy differed by HbA1c, baseline wound size and area and change in wound size per day.

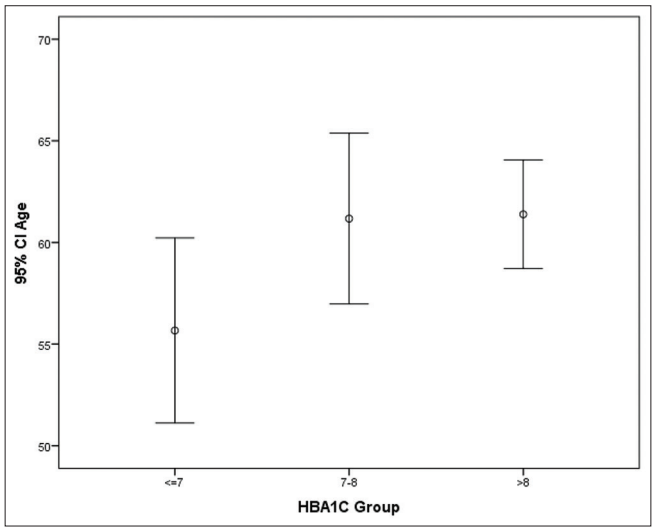

Figure 1: Age distribution

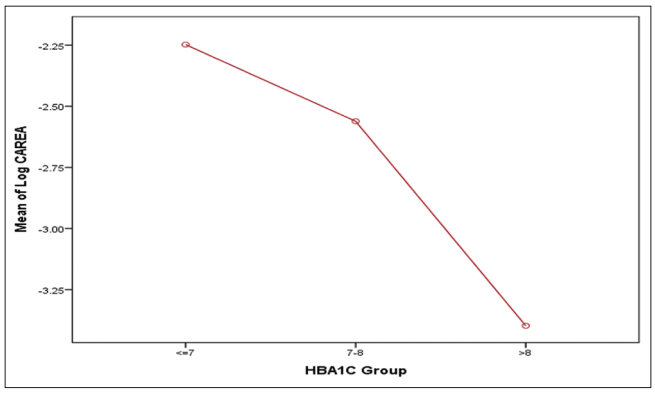

Figure 2: Association of Hba1c with wound area healing rate (log CAREA) in diabetic cutaneous wounds

Mean BMI of our study group was 26.8 which was in the over weight category . Adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and BMI showed there is no statistical significance ($P = 0.664$).

The mean systolic and diastolic BP of our study group were 138 mm of Hg and 78 mm of Hg respectively. Adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and blood pressure values (both systolic and diastolic) showed a borderline significance for diastolic BP ($P = 0.011$) and no statistical significance for systolic BP($P = 0.901$). *P* value which we assigned in our study for statistical significance being <0.001.

Mean ESR in our study group was 6 mm. Adjusted beta coefficients and 95% CI for the relationship between

Table 2: Residential distribution

Residence	HBA1C group				
	≤7	7-8	>8	Chi-square	*P*-value
Rural	16	12	21	1.443	0.486
Urban	23	11	18		
Total	39	23	39		

Table 3: Occupational distribution

Occupation	HBA1C group				
	≤7	7-8	>8	Chi-square	*P*-value
Unemployed	11	8	6	7.063	0.133
Skilled	15	5	10		
Unskilled	13	10	23		
Total	39	23	39		

Table 4: Distribution of smoking status

Smoking	HBA1C group				
	≤7	7–8	>8	Chi-square	*P*-value
Never	15	11	12	6.162	0.187
Former	16	8	11		
Current	8	4	16		
Total	39	23	39		

Table 5: Distribution of alcoholism status

Alcoholism	HBA1C group				
	≤7	7–8	>8	Chi-square	*P*-value
Never	12	11	17	3.785	0.436
Occasional	18	8	11		
Frequent	9	4	11		
Total	39	23	39		

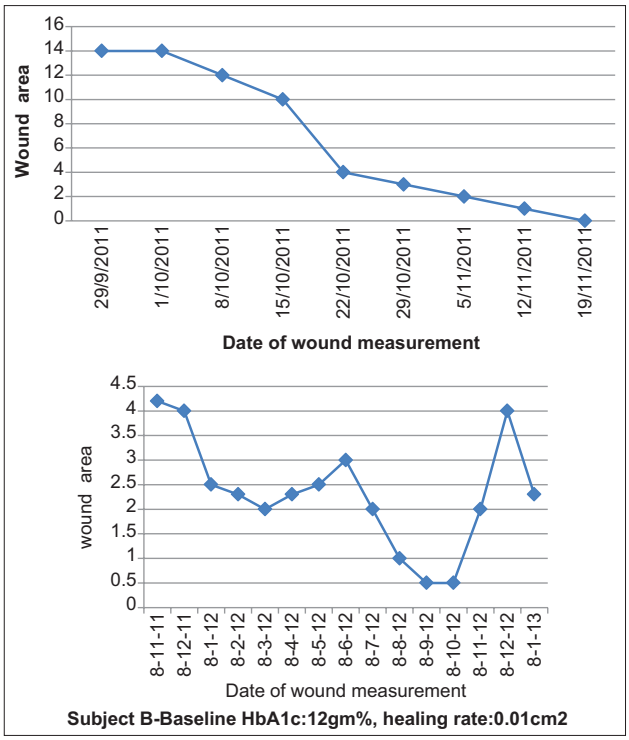

Figure 3: Depiction of wound healing pattern in two diabetic individuals

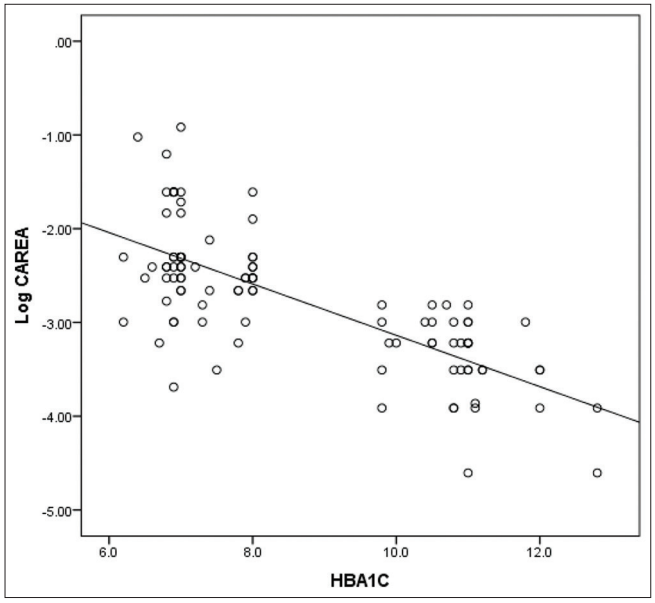

Figure 4: Scatter plot depicting a negative correlation of hba1c and change in wound area per day (log CAREA)

change in wound area per day and ESR showed a statistically insignificant association ($P = 0.220$).

Our results from multiple linear regression models (adjusted beta coefficients and 95% confidence intervals for the relationship between change in wound area per day and other clinical variables) showed HbA1c to have an inverse correlation with wound area healing rate. For each 1.0% point increase in HbA1c, the wound-area healing rate per day decreased by 0.219 cm^2 (95% confidence interval (95% CI): -0.290, -0.148, $P = 0.0001$). Age, sex, Hemoglobin, ESR, smoking, Alcoholism, body mass index, wound number, systolic blood pressure, pulse, white blood cell count, peripheral artery disease, and neuropathy status showed no statistically significant association. Diastolic blood pressure was also inversely associated with wound-area healing rate per day ,but the association was of borderline statistical significance ($P = 0.011$) (P value assigned in our study is $P < 0.001$.) Therefore, the only characteristically significant association with wound-area healing rate per day was for HbA1c. Adjusted beta –coefficients and 95%

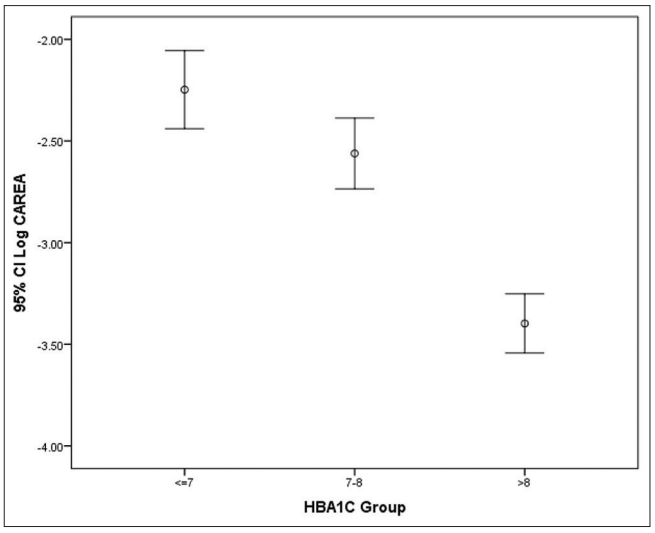

Figure 5: Error plotting showing significance

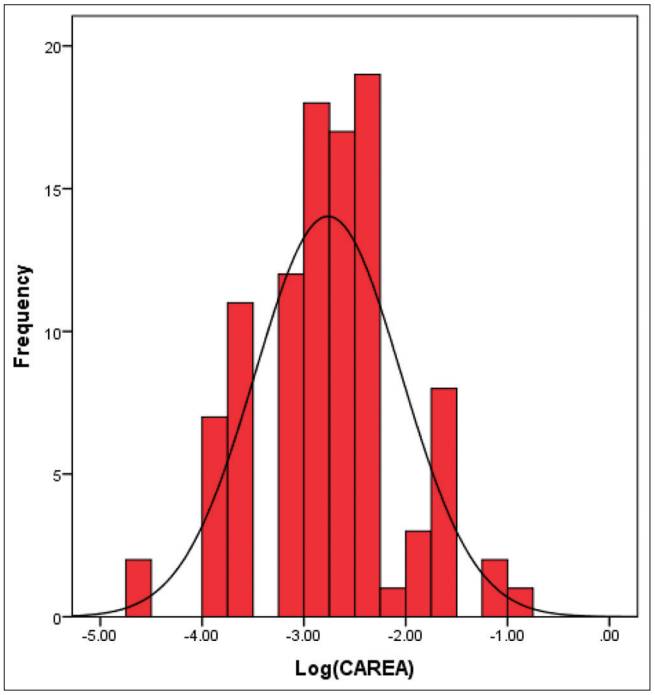

Figure 6: Frequency distribution plot of our study

Table 6: Adjusted beta-coefficients and 95% confidence intervals for the relationship between change in wound area per day and other variables

Patient variable	B	Std. Error	*t*	*P*-value	Lower bound	Upper bound
Constant	–0.668	2.103	–0.318	0.751	–4.851	3.514
Age	–0.003	0.005	–0.657	0.513	–0.013	0.006
BMI	0.027	0.062	0.436	0.664	–0.097	0.151
HBA1C	–0.219	0.036	–6.130	0.000	–0.290	–0.148
SYSTBP	0.000	0.003	–0.124	0.901	–0.007	0.006
DIABP	–0.028	0.011	–2.612	0.011	–0.049	–0.007
PULSE	0.013	0.014	0.887	0.378	–0.016	0.041
WBC	0.000	0.000	–1.279	0.205	0.000	0.000
Hb	0.067	0.058	1.157	0.251	–0.048	0.182
ESR	0.012	0.010	1.235	0.220	–0.007	0.031
WOUNDNO	–0.057	0.072	–0.801	0.426	–0.200	0.085
PAD	–0.199	0.124	–1.607	0.112	–0.444	0.047
RBS	0.002	0.001	1.541	0.127	0.000	0.004
Current Smoker	–0.022	0.122	–0.178	0.859	–0.265	0.221
Alcohol _Frequent	0.149	0.125	1.184	0.240	–0.101	0.398
NEUR	–0.158	0.117	–1.349	0.181	–0.390	0.075

Table 7: Association of Hba1c with wound area healing rate (log CAREA) in diabetic cutaneous wounds

Log CAREA	*n*	Mean	Std. deviation	Std. Error	95% Confidence interval for mean		Minimum	Maximum
					Lower bound	Upper bound		
≤7	39	–2.2477	0.59196	0.09479	–2.4396	–2.0558	–3.69	–0.92
7–8	23	–2.5614	0.40268	0.08396	–2.7355	–2.3872	–3.51	–1.61
>8	39	–3.3979	0.44847	0.07181	–3.5433	–3.2525	–4.61	–2.81
Total	101	–2.7633	0.71788	0.07143	–2.9050	–2.6215	–4.61	–0.92

Table 8: ANOVA testing

Log CAREA	Sum of Squares	df	Mean Square	F	Sig.
Between groups	27.010	2	13.505	53.961	0.000
Within groups	24.526	98	0.250		

confidence intervals for the relationship between change in wound area per day and other variables is shown in Table 6. Association of Hba1c with wound healing rate (log CAREA) in diabetic cutaneous wounds is shown in Table 7. Results of ANOVA testing is shown in Table 8.

Frequency distribution plot of our study showed a normal distribution without skewing of data and we obtained a bell shaped curve. Observed Power of our study being 1.000. Power of study is explained in Table 9.

In our study group 67% had peripheral neuropathy at the time of first examination [Table 10]. In HbA1c >8 gm% category 72% had neuropathy at admission. However, 32% of our study group had features of peripheral arterial disease at the time of admission [Table 11]. Our results from multiple linear regression models for the change in wound area per day shows no statistical significance for peripheral neuropathy ($P = 0.181$) and peripheral arterial disease status ($P = 0.112$). Association of peripheral arterial disease with change in wound area per day (log CAREA) is

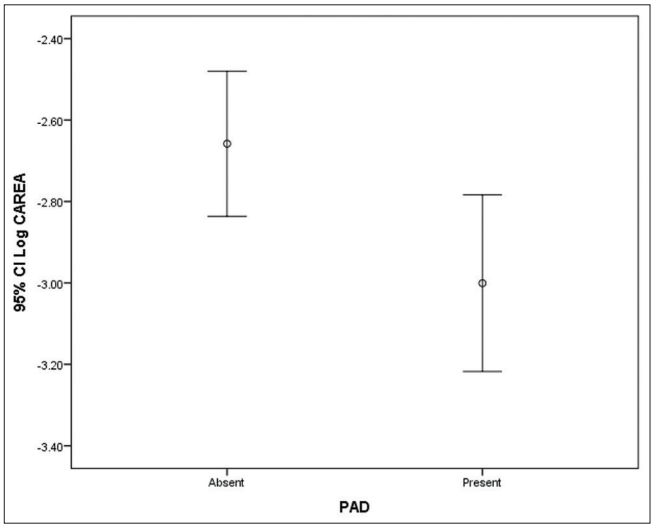

Figure 7: Association of peripheral arterial disease with change in wound area per day (log CAREA)

shown in Figure 7 and Table 12. Table 13 shows association of peripheral arterial disease with change in wound area per day. Assessment of differential healing rate by performing sensitivity analysis stratified by peripheral arterial disease status is shown in Table 14.

To study the possibility of differential healing rates between neuropathic foot wounds that are predominantly diabetic wounds versus wounds in other locations, we performed

Table 9: Power of our study

Dependent variable: Log CAREA			Mean square	F	Sig.	Noncent. parameter	Observed power[b]
Source	Type III sum of squares	df					
Corrected model	27.010[a]	2	13.505	53.961	0.000	107.923	1.000
Intercept	710.785	1	710.785	2840.108	0.000	2840.108	1.000
HBA1C1	27.010	2	13.505	53.961	0.000	107.923	1.000
Error	24.526	98	0.250				
Total	822.735	101					
Corrected total	51.536	100					

Table 10: Distribution of neuropathy status

Neuropathy	HBA1C group				
	≤7	7–8	>8	Chi-square	*P*-value
Absent	15	8	10	1.517	0.468
Present	24	15	29		
Total	39	23	39		

Table 11: Distribution of peripheral arterial disease status

PAD	HBA1C group				
	≤7	7–8	>8	Chi-square	*P*-value
Absent	28	17	25	0.839	0.657
Present	11	6	14		
Total	39	23	39		

Table 12: Association of peripheral arterial disease with change in wound area per day (log CAREA)

Dependent variable	PAD	*n*	Mean	Std. Deviation	Std. Error Mean
Ln_CAREA	Absent	70	–2.6581	0.74731	0.08932
	Present	31	–3.0008	0.59098	0.10614

a sensitivity analysis stratified by wound location and documented neuropathy. For neuropathic foot wounds, each 1.0% point increase in HbA1c was associated with a decrease in wound-area healing rate of -0.306 cm^2 per day ($P = 0.003$). For all other wound locations, each 1.0% point increase in HbA1c was associated with a decrease of -0.261 cm^2 per day ($P = 0.022$). Documented peripheral neuropathy alone was not significantly associated with healing rates, but when combined with HbA1c they are found to be statistically significant. Assessment of differential healing rate by performing sensitivity analysis stratified by neuropathy status is shown in Figure 8 and Table 15. Table 16 shows association of neuropathy status with change in wound area per day.

A sensitivity analysis was also performed stratified by peripheral artery disease status. In participants without peripheral artery disease, HbA1c was not significantly

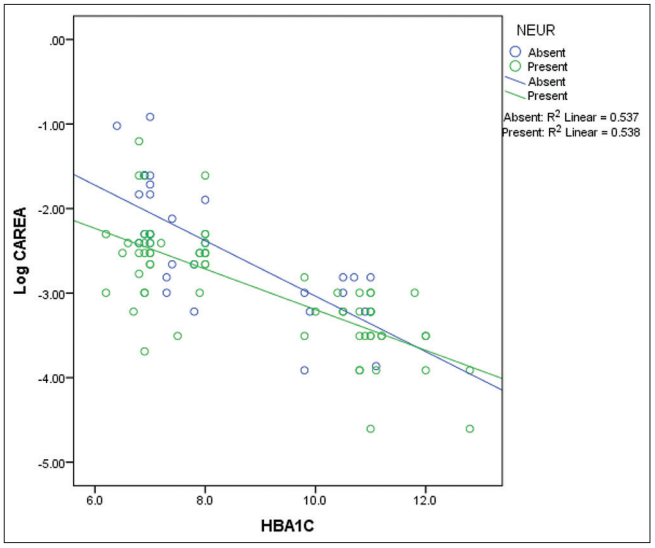

Figure 8: Assessment of differential healing rate by performing sensitivity analysis stratified by neuropathy status

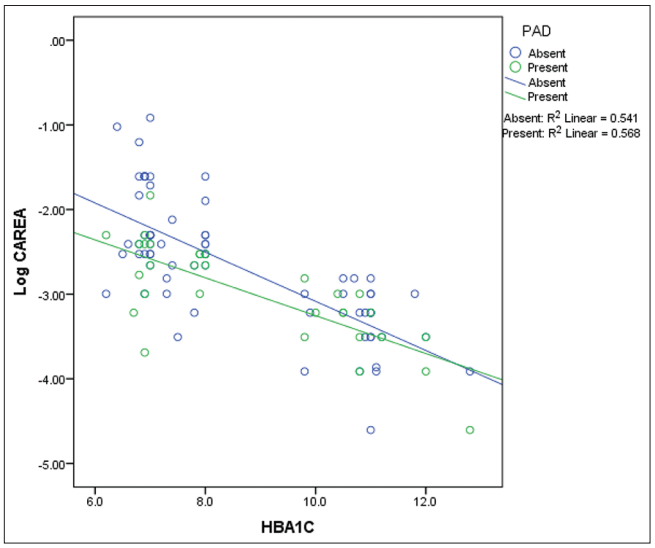

Figure 9: Assessment of differential healing rate by performing sensitivity analysis stratified by peripheral arterial disease status

related to wound-healing rate ($P = 0.026$). In participants with peripheral artery disease, each 1.0% point increase in HbA1c was associated with a decrease of -0.252 cm^2 per day ($P = 0.017$) thereby showing an improvement

Table 13: Association of peripheral arterial disease with change in wound area per day

Ln_CAREA	t	df	*P*-value	Mean difference	Std. error difference	95% Confidence interval of the difference	
						Lower	Upper
Equal variances assumed	2.258	99	0.026	0.34270	0.15180	0.04150	0.64390
Equal variances not assumed	2.470	71.865	0.016	0.34270	0.13872	0.06615	0.61925

Table 14: Assessment of differential healing rate by performing sensitivity analysis stratified by peripheral arterial disease status

Patient variable	B	Std. Error	t	Sig.	Lower bound	Upper bound
Constant	–0.364	0.222	–1.640	0.104	–0.804	0.076
HBA1C	–0.269	0.025	–10.709	0.000	–0.319	–0.219
PAD	–0.252	0.104	–2.423	0.017	–0.458	–0.046

in statistical significance when combined with HbA1c. Assessment of differential healing rate by performing sensitivity analysis stratified by peripheral arterial disease status is shown in Figure 9.

DISCUSSION

According to our study there is definite association between wound healing and HbA1c values. The mean base line area was 4.872 cm^2, and the mean change in area per day was 0.081 cm^2 per day. Despite being the smallest size (3.902 ± 0.198 cm^2) at baseline, wounds at the highest level of HbA1c (>8 gm%) healed at the slowest rate (0.036 ± 0.002 cm^2 per day) .Conversely, ulcers with larger baseline size in the lowest (<7 gm%)(5.305 ± 0.387 cm^2) and intermediate(7-8 gm%) (5.783 ± 0.388 cm^2) HbA1c categories both had greater healing rates than did those with smaller baseline size in the highest HbA1c category. Although there trended to be an inverse association between baseline wound size and healing rate, statistical significance was not reached after adjusting for HbA1c and other variables in our model ($P = 0.213$).

Subjects from rural community who are having their hba1c >8 gm%,which in turn shows a poor glycemic control and lack of diabetic education among subjects hailing from rural background. Strategies should focus on patient education with emphasis on lifestyle modification and compliance with medical therapy.

62.4% of our study group were having smoking addiction in the past (had smoked cigarette/bidis for more than 10 years) of which 28% of the subjects are current smokers. Even though we got an inverse correlation while plotting adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and current smoking status a statistical significant relation was not obtained ($P = 0.859$) [Table 4]. The documented effects of the toxic constituents of cigarette smoke-particularly nicotine, carbon monoxide, and hydrogen cyanide-suggest potential mechanisms by which smoking may undermine expeditious wound repair. Nicotine is a vasoconstrictor that reduces nutritional blood flow to the skin, resulting in tissue ischemia and impaired healing of injured tissue. Nicotine also increases platelet adhesiveness, raising the risk of thrombotic microvascular occlusion and tissue ischemia. In addition, proliferation of red blood cells, fibroblasts, and macrophages is reduced by nicotine. Carbon monoxide diminishes oxygen transport and metabolism, whereas hydrogen cyanide inhibits the enzyme systems necessary for oxidative metabolism and oxygen transport at the cellular level. Compared with non-smokers, smokers have a higher incidence of unsatisfactory healing after facelift surgery, as well as a greater degree of complications following breast surgery. Smokers should be advised to stop smoking prior to elective surgery or when recovering from wounds resulting from trauma, disease or emergent surgery. Adjusted beta coefficients and 95% CI for the relationship between change in wound area per day and current frequent alcoholic status didn't show a statistical significant association ($P = 0.24$).

Our results from multiple linear regression models for the change in wound area per day shows no statistical significance for peripheral neuropathy ($P = 0.181$) and peripheral arterial disease status ($P = 0.112$). These results are consistant with the study of Andrea L *et al*[14] in which they also got a statistical insignificant association for peripheral neuropathy and peripheral arterial disease to change in wound area per day.

The mean base line area was 4.872 cm^2, and the mean change in area per day was 0.081 cm^2 per day. Even the smallest size at baseline, wounds at the highest level of HbA1c (>8 gm%) healed at the slowest rate .Conversely, ulcers with larger baseline size in the lowest (<7 gm%) and intermediate (7-8 gm%) HbA1c categories both had greater healing rates than did those with smaller baseline size in the highest HbA1c category. Although there trended to be an inverse association between baseline wound size and healing rate, statistical significance was not reached after adjusting for HbA1c and other variables in our model ($P = 0.213$).

Table 15: Assessment of differential healing rate by performing sensitivity analysis stratified by neuropathy status

Dependent variable	NEUR	*n*	Mean	Std. Deviation	Std. Error mean	*t*	*P*-value
Ln_CAREA	Present	68	–2.8767	0.70537	0.08554	2.328	0.022
	Absent	33	–2.5296	0.69652	0.12125		

Table 16: Association of neuropathy status with change in wound area per day

Variable	B	Std. Error	t	Sig.
Constant	–0.301	0.22	–1.367	0.175
HBA1C	–0.261	0.025	–10.445	0
NEUR	–0.306	0.102	–3.006	0.003

45.5% of our entire study group comprised of unskilled unemployed subjects, and in that group around 60% had an HbA1c value >8 gm%. Poor glycemic control is more seen in people who are less educated and skilled and in whom diabetic awareness will be scanty.

CONCLUSION

From our entire study conducted at MOSC Medical College, Kolenchery, its been evident that only elevated HbA1c was significantly independently associated with wound-area healing rate. This relationship was stronger for wounds located on the foot, which was insensate neuropathic wounds (67% of all wounds). When our analysis was restricted to these foot wounds, the association with HbA1c remained significant, but when restricted to wounds at all other locations, the association was no longer significant statistically. The relationship was also stronger among participants with peripheral artery disease. Our results suggest that HbA1c is an important clinical predictor of wound-healing rate, particularly in those with neuropathic foot wounds and in those with peripheral artery disease.

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Original Article

A Study of Post-operative Hypocalcemia in Thyroidectomy Patients: Prospective Observational Study

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Abstract

Introduction: The most common metabolic complication that lengthens hospital stay is hypocalcemia after thyroidectomy. The acute and most anticipated complication after thyroidectomy is hypocalcemia. Post-operative hypocalcemia can be acute or irreversible in lifetime supplements, depending on the degree of parathyroid injury.

Aim: This study aimed to analyze the post-operative hypocalcemia in thyroidectomy patients.

Materials and Methods: This prospective study was performed in Dindigul Headquarters Hospital (Tamil Nadu), Department of General Surgery. The study included all patients who underwent thyroidectomy. The data from the patients were obtained after the procedure for the treatment of post-operative hypocalcemia in patients undergoing a detailed thyroidectomy history, careful clinical review, effective radiological, and hematological investigations, including serum calcium and serum albumin and surgical findings.

Results: Out of 75 patients, 68 were female, and 7 were male. Twenty-four patients were in the age group between 12 and 30 years, 23 were in between 31 and 40 years, 18 were between 41 and 50 years, and 10 patients had greater than 50 years. Based on post-operative HPE report 27 patients had Hashimoto's thyroiditis, 14 patients had thyroid adenomas, 13 patients had a nodular goiter, 7 patients had thyroid malignancy, 6 had a toxic multinodular goiter, 4 patients had lymphocytic thyroiditis, and 4 patients had graves diseases. Twenty-six patients had post-thyroidectomy hypocalcemia.

Conclusion: To concluded, from this data that the risk factor for hypocalcemia production is multifactor. The suggested operational technique for preventing permanent hypocalcemia is a thorough dissection and preservation of at least 1 parathyroid gland and its blood supply.

Key words: Hypocalcemia, Incidence, Post-operative complications, Thyroidectomy

INTRODUCTION

A popular treatment performed in the world is a complete thyroidectomy. In patients with thyroid cancer, Graves' disease, and toxic multi-dose goiter, complete thyroidectomy is recommended. In recent years, total thyroidectomy has become an option, particularly in endemic iodine-deficient areas, to treat patients with multinodular goiter. Complete thyroidectomy is usually done when the diagnosis of thyroid lobectomy or lobectomy is performed in the case of a presumed benign condition, such as symptomatic multinodular goiter.[1]

This approach is still associated with hypocalcemia, although safe in experienced hands. Chronic hypoparathyroidism is an extreme and potentially weakening condition caused by several factors. It very frequently happens as a thyroid surgery complication. Certain studies have concluded that the prevalence of intermittent hyperparathyroidism ranges from 6.9% to 46%, whereas hyperparathyroidism rates range from 0.4% to 33%.[2-5]

The risk factors for the risk of predisposing to hypocalcemia after thyroid treatment are giant goiters, complete

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thyroidectomy, chronic goiters, carcinoma, and surgeons' experience, which may lead to devascularization or accidental removal of the parathyroid glands.[4,6,7] Hypocalcemia can occur secondary to surgical trauma, devascularization, and unintended extraction of the glands. The length of stay after thyroidectomy often depends primarily on the development of hypocalcemia. In most cases, hypocalcemia post-thyroidectomy is reversible, although it can take several months.

A small number of cases (0–12%) remain during this time and are assumed to be permanent, even though the gap between temporary and permanent hypocalcemia ranges from 6 months to 1 year.[8] However, the patient is committed to lifelong symptomatic care with calcium or vitamin D if the interval is permanent. The surgeon needs to make every effort to maintain one or more sustainable parathyroid, especially in the case of total thyroidectomy or subtotal thyroidectomy to avoid this complication.[9]

Careful dissection and protection of parathyroid glands and their blood supply are recommended as an organizational strategy.[5] Parathyroid glands must be correctly identified to help prevent accidental excision. Where less than three glands are found during the procedure, the probability of complication is higher.[4]

Factors that can reliably predict the development of post-thyroidectomy hypocalcemia can help start calcium supplements early and adequately and predict patients' protection from early release.[10] In several studies, the occurrence of post-thyroidectomy hypocalcemia was correctly predicted by post-operative parathyroid hormone (PTH), which was lower than the value intraoperatively, or on the same day of the surgery, between 8 and 15 Pg/mL.

Aim

This study aimed to analyze the post-operative hypocalcemia in thyroidectomy patients.

MATERIALS AND METHODS

This prospective study was performed in Dindigul Headquarters Hospital (Tamil Nadu), Department of General Surgery. The study included all patients who underwent thyroidectomy. The data from the thyroidomes were obtained after the procedure for the treatment of post-operative hypocalcemia in patients undergoing a detailed thyroidectomy history, careful clinical review, effective radiological, and hematological investigations, including serum calcium and serum albumin and surgical findings. The primary pathology of parathyroid patients undergoing hemi-thyroidectomy/lobectomy. To prevent previously altered parathyroid functions, we excluded patients with altered pre-operative levels of calcium and excluded patients with prior radiation history, including those with a calcium supplement already excluded. We have followed all patients who meet our serum calcium requirements after operating on day 1, day 2, and day 4. We have also reported a history of various post-operative hypocalcemia presentations such as perioral stunning, carpopedal spasm, trousseau sign, Chvostek's signs, ECG changes in hypocalcemia, and other neurological symptoms.

RESULTS

Out of 75 patients, 7 patients were male, and 68 patients were female [Figure 1].

Based on the age group, 24 patients were in the age group between 12 and 30 years, 23 were between 31 and 40 years, 18 were between 41 and 50 years, and 10 patients had greater than 50 years [Figure 2].

Based on the pre-operative indication for total thyroidectomy, 12 patients had malignancy, 19 patients had toxic features, and 44 patients had swelling/goiter [Figure 3].

Based on the surgery's nature, 72 patients had a total thyroidectomy and 3 patients had re-surgery/complete thyroidectomy [Figure 4].

Based on post-operative HPE report, 27 patients had Hashimoto's thyroiditis, 14 patients had thyroid adenomas, 13 patients had a nodular goiter, 7 patients had thyroid malignancy, 6 had a toxic multinodular goiter, 4 patients had lymphocytic thyroiditis, and 4 patients had graves diseases [Figure 5].

Based on post-operative hypocalcemia, 26 patients had hypocalcemia and 49 patients had no hypocalcemia [Figure 6].

Out of 26 patients had post-operative hypocalcemia, 4 were male and 2 were female. Six patients had an age between 12 and 30 years, 9 patients had an age between 31 and 40 years, 4 patients had an age between 41 and 50 years, and 7 patients had age greater than 50 years. Nine patients had malignancy, 9 patients had toxic features, and 8 had swelling/goiter. Twenty-three patients had a total thyroidectomy and 3 patients had re-surgery/completion thyroidectomy. Based on post-operative HPE report, 6 patients had Hashimoto's thyroiditis, 3 patients had thyroid adenomas, 4 patients had a nodular goiter, 7 patients had thyroid malignancy, 3 had toxic multinodular goiter, and 3 patients had graves diseases [Table 1].

DISCUSSION

The most common issue after TT is hypocalcemia which may be temporary or permanent.[11] Temporary hypocalcemia may be either biochemically (BH) or symptomatically (SH), usually 24–48 h post-thyroidectomy.[12] Hence, patients must be monitored for this time before discharge to avoid the development of clinically relevant hypocalcemia. The poor rural health care system is especially significant in India. Production of hypocalcemia after complete thyroidectomy (TT) depends on different factors. One of them was serum calcium levels postoperatively.[13]

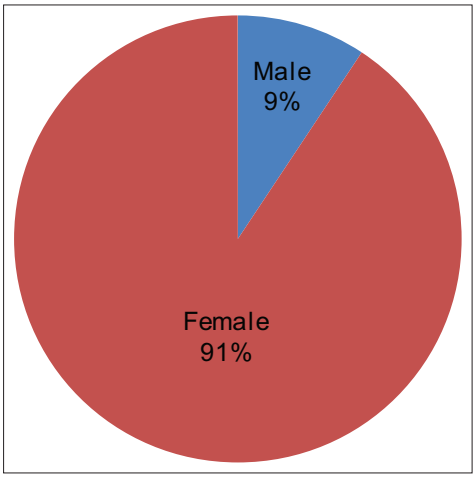

Figure 1: Gender distribution

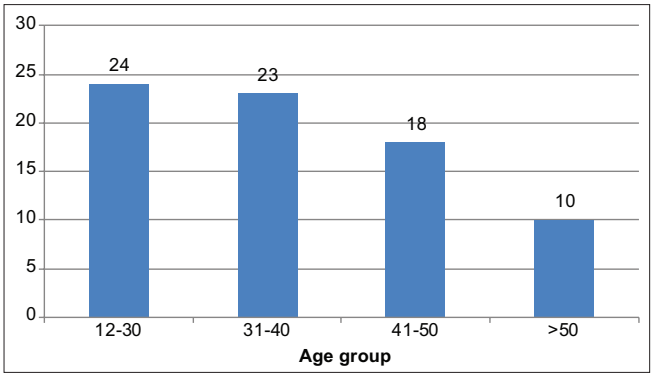

Figure 2: Age distribution

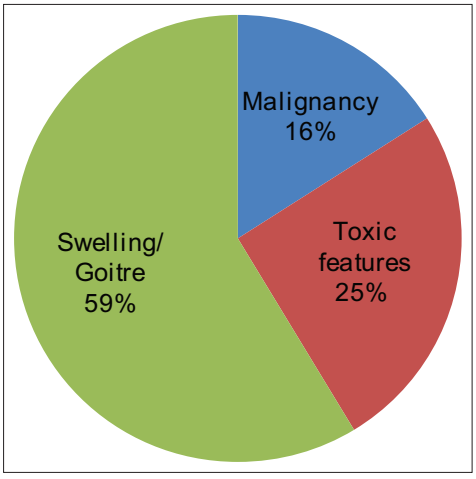

Figure 3: Indication for total thyroidectomy

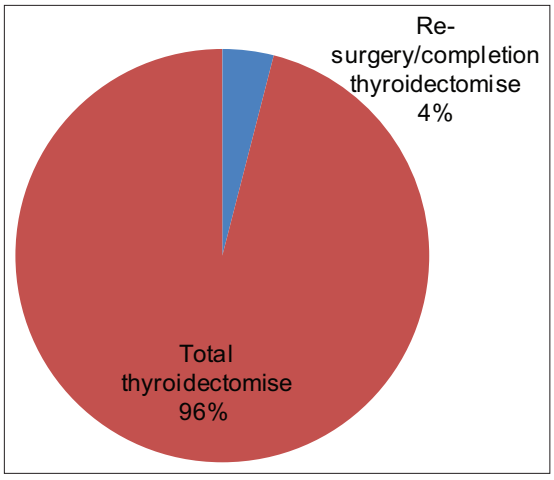

Figure 4: Distribution of nature of surgery

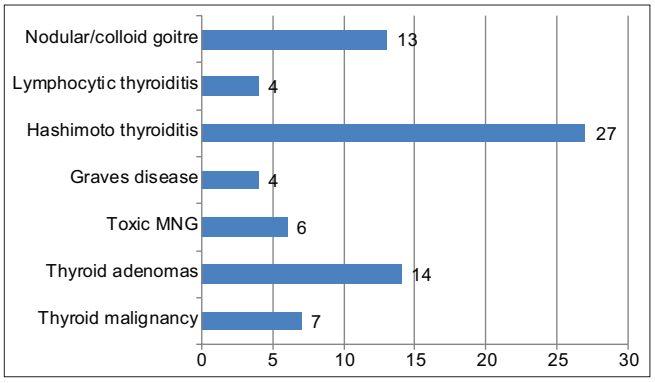

Figure 5: Post-operative final diagnosis based on HPE report

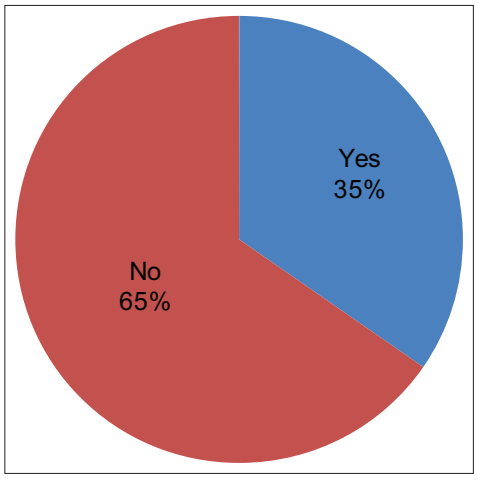

Figure 6: Post-operative hypocalcemia

Table 1: Distribution of post-operative hypocalcemia

Variables	Post-thyroidectomy hypocalcemia
Gender	
Male	4
Female	22
12–30	6
Age group	
31–40	9
41–50	4
>50	7
Indications	
Malignancy	9
Toxic features	9
Swelling/goiter	8
Nature of surgery	
Re-surgery/completion thyroidectomise	3
Total thyroidectomise	23
Diagnosis	
Thyroid malignancy	7
Thyroid adenomas	3
Toxic MNG	3
Graves' disease	3
Hashimoto thyroiditis	6
Nodular/colloid goiter	4

A prospective study by Sperlongano *et al.* observed hypocalcemia in 27 out of 180 patients following thyroidectomy in total with 40.7%, 22.2%, 29.6%, 3.7%, and 3.7% -, 2nd-, 4th-, and 5th-day, hypocalcemia in all cases.[14]

In another prospective study of 102 Pasque *et al.* patients, 18 patients experienced hypocalcemia, 38.8% on the 1st day after surgery, 22.2% on the 2nd day after surgery, and 33.3% on the third day off and 5.5% on the 4th day after the surgery.[15]

Tredici *et al.* recorded a 50% hypocalcemia incidence for patients with total thyroidhomes on the 1st post-operative day, 46% on the second day, 22% on the third day, and the remaining patient's hypocalcemia on the 4th and 5th post-operative days.[16]

Asari *et al.* performed a study to determine whether serum calcium measurements would forecast hypoparathyroidism on 1–4 post-operative days. They observed that the assessment of serum calcium on a second, (62.8%) and fourth, and (32.6%) post-operative days was of the highest hypoparathyroidism sensitivity (72.1%), as opposed to the first (18.6%).[17]

CONCLUSION

We inferred from this analysis that the risk factor for hypocalcemia production is multifactor. The suggested operational technique for preventing permanent hypocalcemia is a thorough dissection and preservation of at least one parathyroid gland and its blood supply.

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Original Article

Outcome of Collagen Dressing in Partial Thickness Burns Patients: An Observational Study

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Abstract

Introduction: In both adults and children, burn injuries are a major public health issue. Burn burns are very painful and typically slowly healing and scarring conditions. To treat burn wounds, dressings play a crucial function.

Aim: The aim of this study was to analyze the outcome of collagen dressing in partial thickness burns patients.

Materials and Methods: This prospective study was performed in Dindigul Headquarters Hospital (Tamil Nadu), Department of General Surgery. Wound examination was performed and all patients were treated with wound swab before collagen was added. The analyzed variables included pain score, infection rate, wound healing rate, resulting scar, and patient conformity.

Results: Out of 100 patients, 64 were male and 36 were female. Based on burns percentage, 18 patients had 10% burns wound, 14 patients had 15% burns wound, 26 patients had 20% burns wound, 17 patients had 25% burns wound, 7 patients had 30% burns wound, 8 patients had 35% burns wound, and 10 patients had 40% burns wound. Mean age was 42.28 years, mean pain score was 2.21 ± 0.98, mean time taken for healing 12.31 ± 4.12 days, patient compliance was 93%, healing without infection was 92%, and good scar formation was 100%.

Conclusion: Collagen sheet facilitates early recovery, decreases the need for painkillers, and reduces the occurrence of related complications, such as infections.

Key words: Collagen, Dressing, Partial thickness burns

INTRODUCTION

In both adults and children, burn injuries are a major public health issue. Thermal burns, scalding, or direct contact with warm surfaces are the frequent causes of burn injuries. Burn injuries are normal in kids since thinner skin tolerates a smaller time with less heat before full thickness injury happens.[1] If moist wound bed and sufficient drainage are preserved and no infection remains, a deep partial thickness injury is able to cure. In the absence of the above-mentioned causes, a partial burn wound becomes a total thickness wound.[2]

Most children suffer from burns involving small areas; 80% of burns occur in children below 5 years old, with hot spillages of the majority.[3] A bacterial infection which delays healing and increases pain, as well as the risk of scarring, is one of the key issues with the management of burns.

Burning injuries are the cause in great quantities in both the wound and other tissues for the release of inflammatory mediators. They often contribute to blood vesicles being limited and extended, and the capillary penetration and edema increase significantly. The generalized edema occurs in burned and unburnt skin, in response to changes in starling forces caused by burns. Initially, the hydrostatic pressure of the interstitial skin is markedly decreased. The interstitial pressure rises marginally in the unburned skin. The loss of protein due to the increased capillary permeability raises the interstitial oncotic pressure and the plasma oncotic pressure. The generalized edema happens as a result of these events. The edema is greater in the blamed tissues, as the interstitial pressure is lower.

In extracellular connective tissue, the most essential fibrous protein is the collagen. Collagen is the most abundant and

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all-around protein in the entire animal kingdom. The term collagen was derived from the Greek word "kola," which means glue plus gene. Of the total protein in the human body, 25% is made up of collagen and about 70–80% is made up of skin. Scientists have gained significant interest in the use of collagen for collagen in recent decades. Various dressing materials such as calcium alginate, hydro-colloid membranes, and fine mesh gas were produced during the last decade. They have an inconvenience since they are bacteria permeable. Biological dressings such as collagen on the other hand create a physiological interface between a wound surface and the environment, and they are impervious to bacteria.[4] In terms of easing of use and safe, non-immunogenic, non-pyrogenic, hypoallergenic, and pain-free, the collagen dressings have other advantages compared with traditional dressings.[5,6]

Aim

The aim of this study was to analyze the outcome of collagen dressing in partial thickness burns patients.

MATERIALS AND METHODS

This prospective study was performed in Dindigul Headquarters Hospital (Tamil Nadu), Department of General Surgery. Inclusion criteria: All patients with partial burns of partial thickness of (1st and 2nd grade), <40% of the surface area of the body. Not <24 h of wounds was charred. Inclusion criteria: Patients with full thickness burns, patients with burns with a surface area of >40%. Electric and non-thermal burning patients. Patients are older than 24 h with burn wounds. xamination was performed and all patients were treated with wound swab before collagen was added. Patients with <40% of the total body surface area in partial thickness burns shall be measured. Cases have been treated with dressing in collagen. Time, discomfort, consistency of cure, infection, and compliance with the patient are evaluated in cases. Results obtained based on: The pain score is based on the patient's own words as a subjective pain. The ranking is 0–10 visually analog. After 24 h of dressing use, the pain score is elicited. 0 means no pain and 10 refer to the highest pain that the patient can handle.

RESULTS

Out of 100 patients 64 were male and 36 were female [Figure 1].

Based on burns percentage, 18 patients had 10% burns wound, 14 patients had 15% burns wound, 26 patients had 20% burns wound, 17 patients had 25% burns wound, 7 patients had 30% burns wound, 8 patients had 35% burns wound, and 10 patients had 40% burns wound [Figure 2].

Mean age was 42.28 years, mean pain score was 2.21 ± 0.98, and mean time taken for healing 12.31 ± 4.12 days [Table 1].

Patient compliance was 93%, healing without infection was 92%, and good scar formation was 100% [Figure 3].

8% of infections were reported in the study [Figure 4]. 100% of patients had shown good scare [Table 2].

DISCUSSION

Deterred areas are therefore delayed by the exposure of susceptible areas of subcutaneous tissues to infection. A layer of collagen is necessary to serve for the orderly growth of the epithelium as the ground upon which it grows and arranges. Denuded areas cannot adequately provide for this, resulting in large scars and even keloids. The intact epithelium provides a protective shield against cutaneous nerves otherwise the nerves are exposed and painful. Wounds left uncovered are vulnerable to infection and more health complications. The rate of infection and the degree of contraction have been well reported to be

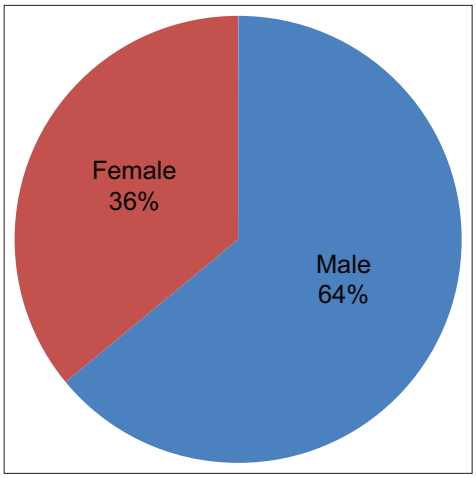

Figure 1: Gender distribution

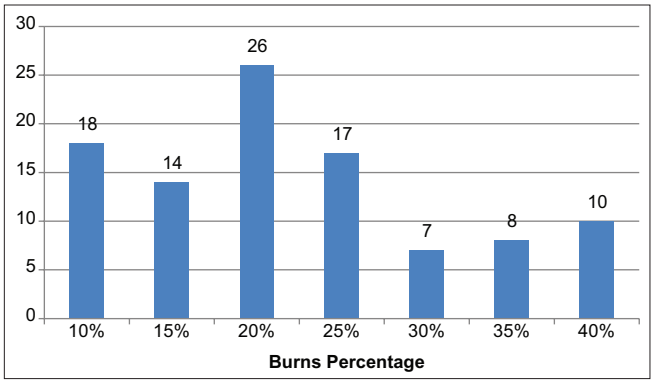

Figure 2: Burns percentage

Table 1: Distribution of various parameters

Parameters	Mean value
Age	42.28 years
Pain score	2.21±0.98
Healing time	12.31±4.12 days

Table 2: Distribution of various parameters

Parameter		Frequency	Percentage
Infection	Absent	92	92
	Present	8	8
Compliance	Good	93	93
	Bad	7	7
Scar	Good	100	100

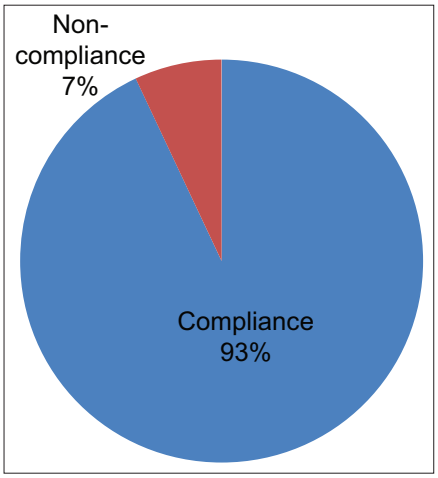

Figure 3: Compliance

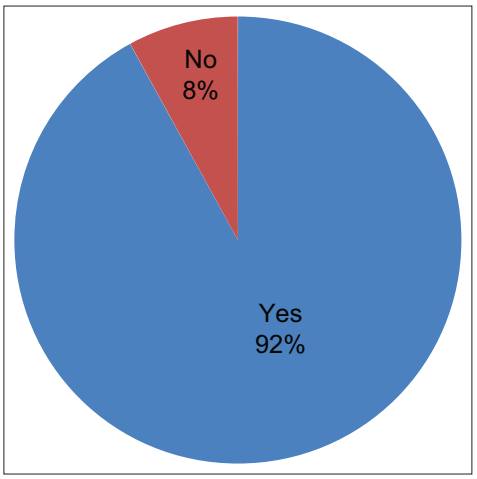

Figure 4: Infection

substantially decreased if injuries are dressed as biological materials rather than exposed or non-biological in cures. Xenogeneic collagen membrane has been found to be ideal for lining mucosa and skin, that is, soft and wound-adaptable, regardless of contour.[7-10]

In our sample, 8% of patients were infected which indicated a lower rate of collagen dressing infection. None of the cases showed any adverse effects on collagen and proved its safety. This result is similar to Gupta RL study.[11]

In our study, the average healing time was 12.31 days. This shows that dressing collagen helps to minimize the time for cure. The Gupta RL research, which reveals a healing time of 10–14 days, was consistent with this results.[11]

About 100% of collagen dressing patients had healthy scars in our study. Collagen thus helps to remodel the tissue and provides a stronger scar than other dressings. That is the same as Demling RH analysis.[12]

Collagen dressing patient compliance was strong at 93%. Therefore, collagen dressing had a higher degree of conformity observed. This finding was in line with Gerding RL analysis.[13]

CONCLUSION

Collagen sheet facilitates early recovery, decreases the need for painkillers, and reduces the occurrence of related complications, such as infections. In most people with collagen, the patient's morbidity is decreased as the resulting scar is strengthened. During a partial thickness burn, collagen may be used as a temporary biological dressing material because of its easy applications and good membrane tolerance.

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Original Article

Farrago of Pediatric Solid Malignancies from a Tertiary Care Centre in Northeast India: A Retrospective Analysis

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Abstract

Background: Worldwide, the annual number of new childhood cancer exceeds 200,000 and >80% of these are from the developing world. Cancer remains the leading cause of disease-related mortality in children.

Aim and Objective: This study aimed to throw light on the prevalence and pattern of pediatric solid malignancies at a tertiary care center in Northeast India.

Materials and Methods: A retrospective analysis of pediatric solid malignancies in the age group of 0–14 years was carried out over a period of 1 year in the department of pathology.

Results: Forty-five cases of pediatric solid malignancies were identified. The mean age of the study group was 7.7 years with the peak age incidence in the >9–14 years of age group, and male to female ratio being 1.1:1. The top tumors in the list were lymphomas (20%), retinoblastomas (13.3%), soft-tissue sarcomas, and germ cell tumors (11.1% each), bone sarcomas and neuroblastomas (8.9% each), and central nervous system tumors (6.9%). Lymphomas and retinoblastomas were, respectively, the most common solid malignancies in boys and girls. Equal sex distribution was detected in bone sarcomas, neuroblastomas, and salivary gland tumors, while the other tumors exhibited gender predilection. Epithelial malignancies such as salivary gland carcinoma, nasopharyngeal carcinoma, and rarer ones such as adrenal cortical carcinoma were also chronicled.

Conclusion: Accurate diagnosis of these entities aided by meticulous histopathological evaluation serves as a medium for compilation of data regarding these malignancies. Information provided by this study can aid in reflecting the tumor burden and boosting the public health-care strategies.

Key words: Cancer, Childhood, Pattern, Histopathology, Lymphoma

INTRODUCTION

Children are not merely adults, and the diseases they contract are not merely variants of adult disease. Neoplasia of childhood is one such "disease" which occupies a numerically important group leading to untimely deaths in the growing age group and taking a heavy toll in terms of lives. Neoplasia in childhood are unique to, or at least take distinctive forms in this stage of life. Only 2% of all malignant tumors occur in infancy and childhood; nonetheless, cancer is a leading cause of death in children aged 4–14. Neoplastic disease accounts for approximately 9% of all deaths in this cohort.[1] About 30.76% of the Indian population falls in the 0–14 years of age group.[2] The overall incidence rates of childhood cancer across the world vary between 75 and 150 per million children per year, while the reported age of the standardized incidence rate for India ranges from 38 to 124 per million children per year, amounting to 1.6–4.8% of all cancers in India.[3] In the developing world childhood cancers are yet to be recognized as a major pediatric illness due to several other competing causes of death such as diarrheal illness and respiratory illness. However, due to

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considerable reduction in infant and child mortality rate, it is emerging as a distinct entity to be dealt with. Rapid and accurate diagnosis of childhood tumors and hematological malignancies has become increasingly important as more specific chemotherapeutic regimes have evolved. The prognosis of malignancy in children depends primarily on the tumor type, extent of disease at diagnosis, and rapidity of response to treatment. Data reporting in India is still in its nascent stage, especially for pediatric malignancies. Cancer registries that document the incidence of disease are plagued by poor reporting from government hospitals and no reporting by many of the private practitioners, with some population based studies reporting an incidence of just over a 1000 cases in 10 years. To enhance this data, this study was undertaken as an endeavor to depict the prevalence and pattern of pediatric solid malignant tumors presenting at a tertiary care center in Northeast India.

MATERIALS AND METHODS

A retrospective analysis of pediatric solid malignancies was carried out over a period of 1 year in the department of pathology at a tertiary care center in Northeast India following all the guidelines of the institutional ethics committee. Only those cases in children between the age group of 0 and 14 years with conclusive and unequivocal diagnosis were included in the study. Details of age, gender, and other relevant clinical information were collected from the medical records. The hematoxylin and eosin stained slides sectioned from formalin fixed paraffin embedded tissues and the immunohistochemistry stained slides were retrieved from the archives in the department of pathology and evaluated.

RESULTS

The study consisted of 45 cases of solid pediatric malignant tumors who had presented at our institute during a period of 1 year [Table 1]. The annual incidence rate of pediatric solid malignancies was 0.8% of total pediatric admissions. The mean age of the childhood solid tumors was 7.7 years with the peak age incidence in the >9–14 year age group (44.4%). Male cases (24, 53.3%) outnumbered females (21, 46.7%). The most common pediatric solid malignancy was

Table 1: Distribution of histological subtypes of pediatric solid malignancies

SL No.	Tumor type	Frequency, *n* (%)	Mean age, years	Age group, *n* (%)			Gender, *n* (%)	
				0–4 years	>4–9 years	>9–14 years	Male	Female
1.	Lymphoma	9 (20)	9.9	1 (11.1)	3 (33.3)	5 (55.6)	8 (88.9)	1 (11.1)
(a)	T-Lymphoblastic lymphoma	5 (55.6)	10	0	3 (60)	2 (40)	4 (80)	1 (20)
(b)	DLBCL	2 (22.2)	13	0	0	2 (100)	2 (100)	0
(c)	Classical Hodgkin lymphoma	2 (22.2)	6.5	1 (50)	0	1 (50)	2 (100)	0
2.	Retinoblastoma	6 (13.3)	4.3	3 (50)	3 (50)	0	1 (16.7)	5 (83.3)
3.	Soft tissue sarcoma	5 (11.1)	10	0	1 (20)	4 (80)	5 (100)	0
(a)	Rhabdomyosarcoma	2 (40)	11	0	0	2 (100)	2 (100)	0
(b)	Ewing Sarcoma/PNET	1 (20)	5	0	1 (100)	0	1 (100)	0
(c)	Fibrosarcoma	1 (20)	12	0	0	1 (100)	1 (100)	0
(d)	Synovial sarcoma	1 (20)	11	0	0	1 (100)	1 (100)	0
4.	Germ cell tumor	5 (11.1)	10.6	1 (20)	0	4 (80)	1 (20)	4 (80)
(a)	Yolk sac tumor	2 (40)	8.5	1 (50)	0	1 (50)	1 (50)	1 (50)
(b)	JGCT	1 (20)	11	0	0	1 (100)	0	1 (100)
(c)	Dysgerminoma	1 (20)	13	0	0	1 (100)	0	1 (100)
(d)	MMGCT	1 (20)	12	0	0	1 (100)	0	1 (100)
5.	Neuroblastoma	4 (8.9)	4.75	2 (50)	2 (50)	0	2 (50)	2 (50)
6.	Bone malignancies	4 (8.9)	4.75	0	0	4 (100)	2 (50)	2 (50)
(a)	Ewing sarcoma/PNET	2 (50)	11.5	0	0	2 (100)	0	2 (100)
(b)	Osteosarcoma	2 (50)	13.5	0	0	2 (100)	2 (100)	0
7.	CNS malignancies	3 (6.9)	12.5	1 (33.3)	2 (66.7)	0	0	3 (100)
(a)	Medulloblastoma	2 (66.7)	3	1 (50)	1 (50)	0	0	2 (100)
(b)	Immature pineal teratoma	1 (33.3)	8	0	1 (100)	0	0	1 (100)
8.	Wilms' tumour	2 (4.4)	2	2 (100)	0	0	0	2 (100)
9.	LCH	2 (4.4)	5.25	1 (50)	1 (50)	0	2 (100)	0
10.	Salivary gland carcinomas	2 (4.4)	14	0	0	2 (100)	1 (50)	1 (50)
(a)	Mucoepidermoid carcinoma	1 (50)	14	0	0	1 (100)	0	1 (100)
(b)	Adenoid cystic carcinoma	1 (50)	14	0	0	1 (100)	1 (100)	0
11.	Hepatoblastoma	1 (2.2)	1	1 (100)	0	0	0	1 (100)
12.	UN NPC	1 (2.2)	8.5	0	1 (100)	0	1 (100)	0
13.	Adrenal cortical carcinoma	1 (2.2)	13	0	0	1 (100)	0	1 (100)
14.	Total	45	7.7	12 (26.7)	13 (28.9)	20 (44.4)	24 (53.3)	21 (46.7)

DLBCL: Diffuse large B cell lymphoma, JGCT: Juvenile granulosa cell tumour, MMGCT: Malignant mixed germ cell tumour, CNS: Central nervous system, LCH: Langerhans cell histiocytosis, UN NPC: Undifferentiated non-keratinizing nasopharyngeal carcinoma

the lymphomas (20%), followed by retinoblastoma (13.3%), soft-tissue sarcomas (STS), and germ cell tumors (11.1% each); bone sarcomas and neuroblastomas (8.9% each), and central nervous system (CNS) tumors (6.9%) completed the top five. Moreso, lymphomas were the most common solid malignancy in boys, while retinoblastoma topped the list in girls. Equal sex distribution was detected in the sarcomas of bone, neuroblastomas, and salivary gland tumors, while other tumors exhibited sex predilection [Figure 1]. Lymphomas comprised nine cases, out of which seven were Non-Hodgkin lymphomas (NHL) and two were Hodgkin lymphomas (HL). As far as the overall age incidence of lymphoma was concerned, most of the cases (5) were in the >9–14 years of age group (55.6%), with NHL accounting for four of those. The 0–4 years of age group reported the lowest incidence, with only one case of HL and none of NHL in that category. Lymphomas showed a predilection for boys, with the male to female ratio being 8:1. NHL constituted six out of the total eight cases in males as well as for the lone female case. With regards to the histologic type, the predominant sort was T-lymphoblastic lymphoma (5 cases, 71.4%), followed by diffuse large B-cell lymphoma (2 cases, 28.6%). Both the HL belonged to the mixed cellularity group. While bone marrow involvement was not detected in both the cases of HL, three out of seven cases of NHL (42.9%) evinced metastasis to the bone marrow.

The present study involved six cases of retinoblastoma, accounting for 13.3% of the total cases. Retinoblastoma was the most common solid tumor in girls, with five female cases. STS came joint third, comprising five cases (11.1%), all of them occurring in boys. Majority of those patients (4 cases) were above 9 years, an overwhelming incidence rate of 80% in the >9–14 year age group. Morphologically, the five cases of STS comprised two cases of embryonal rhabdomyosarcoma and one case each of fibrosarcoma of the hand, synovial sarcoma of the scalp and extraskeletal Ewing sarcoma/Primitive neuroectodermal tumor (ES/PNET) of the shoulder. Germ cell tumors (GCT) totalled five cases (11.1%), ranking joint third along with STS. All the GCTs were of gonadal origin, comprising two cases of yolk sac tumor, and one case each of dysgerminoma, juvenile granulosa cell tumor and malignant mixed germ cell tumor. Neuroblastoma numbered four cases (8.9%) and had an equal sex distribution, with the male cases occurring in the >4–9 years of age group and the female cases in the 0–4 years of age group. Bone marrow involvement was detected in three out of the four cases. Bone malignancies equalled neuroblastoma cases (4 cases, 8.9%), two cases each of osteosarcoma (both in males) and ES/PNET (both in females). CNS tumors accounted for three cases (6.9%), comprising two cases of medulloblastomas and one case of immature pineal teratoma. Wilms tumor comprised 2 cases in the present study (4.4%), both involving the left kidney. Completing the list were two cases each of Langerhans cell histiocytosis (LCH), and salivary gland malignancies (adenoid cystic carcinoma and mucoepidermoid carcinoma), followed by lone case each of hepatoblastoma, adrenal cortical carcinoma (ACC), and non-keratinizing undifferentiated nasopharyngeal carcinoma.

DISCUSSION

Data regarding the incidence of childhood solid tumors is limited. Although children <15 years comprise 31% of the Indian population, the exact incidence of most childhood solid tumors in India is not known. Lack

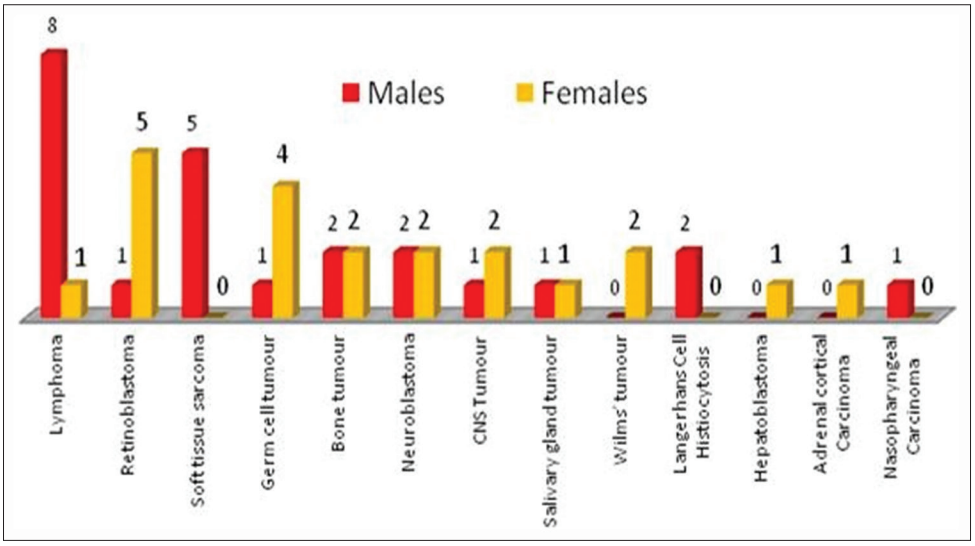

Figure 1: Gender distribution of pediatric solid malignancies in the study

of information among patients and parents about the signs and symptoms of childhood cancer, relying on nonmedical forms of treatment, lack of finances, untrained professionals at a primary care center, lack of laboratory and diagnostic imaging equipment, poor data collection, and reporting infrastructure all lead to suboptimal reporting.[4] Appropriate management of pediatric tumors requires complete epidemiological data of pediatric tumors in different geographical areas. In India, cancer is the 9th common cause for the deaths among children between 5 and 14 years of age.[5] Indian cancer registries have reported the proportion of childhood cancers relative to all cancers in the range of 0.8–5.8% in boys and 0.5–3.4% in girls.[6] The present study collected a database of pediatric malignant solid tumors from a tertiary care center in the most north eastern part of India with the aim of analyzing the patterns and frequency of these tumors.

The 45 cases of pediatric solid malignancies in this study formed 0.8% of all pediatric admissions in the hospital. This finding is quite in agreement with that of the results of Upadhyay *et al.* and Miglani *et al.*[7,8] The slightly increased incidence rate in the present series can be a reflection of the rising trend of childhood solid tumors in our country. The peak age incidence was in >9–14 years of age group (44.4%), which is comparable to that found by Jain *et al.*, Gupta *et al.*, and Sharma *et al* [Table 2].[8-10] Embryonal tumors such as neuroblastoma, Wilms tumor, and retinoblastoma occurred mainly in the 0–4 years of age group, while the >9–14 years of age group mainly consisted of lymphomas, sarcomas, germ cell tumors, and carcinomas. The overall incidence of childhood malignant tumors is more in males (male to female ratio of 1.1:1). This observation has been made uniformly in literature by many authors.[6,8-17] However, some tumors such as retinoblastoma, Wilms tumor, and germ cell tumors tend to show a slight female preponderance. The reported incidence of childhood cancer in India in males (39–150 per million children per year) is higher than in females (23–97 per million children per year) in all population-based cancer registries except in Northeast India.[9]

Table 2: Peak age incidence group of pediatric solid malignancies in various studies

SL. No.	Series	Peak age incidence group
1.	Miglani *et al.*	0–5 years
2.	Bannerjee *et al.*	0–5 years
3.	Jain *et al.*	10–13 years
4.	Gupta *et al.*	11–15 years
5.	Pandey *et al.*	10–14 years
6.	Hesham *et al.*	0–4 years
7.	Memon *et al.*	0–4 years
8.	Sharma *et al.*	12–19 years
9.	Present study	>9–14 years

The pattern of pediatric solid malignancies in various studies has been enlisted in Table 3. Most of the studies arrayed including the current one depict lymphomas as the most common childhood solid tumors. Shah *et al.*, Agboola *et al.*, and Ibrahim *et al.* also bear witness to that.[18-20] The incidence in the current context was 20%, which is almost similar to the findings of Sharma *et al.* and Upadhyay *et al.*[6,17] In fact, Hesham *et al.* in a study of 155 solid pediatric malignancies from Egypt discerned a rather high incidence (48.4%) of lymphomas.[13] The distribution of NHL and HL varies among different series [Table 4]. Some have found NHL to be in the majority,[13,21-24] while in some studies HL predominated.[9,12,14] NHL was more common in the present series. Majority of the lymphoma patients were in the >9–14 year age group, which is similar to the observation by Surveillance, Epidemiology, and End Results (SEER), Mankodi *et al.*, Jain *et al.*, and Baneerjee *et al.*[8,11,25,26] Moreover, it can be stated that lymphoma does not spare any age group. Lymphoid neoplasms predominated in boys, with the male to female ratio varying in different series.[6,8,9,11-14] Contrary to the west, lymphoblastic lymphomas and diffuse large B cell lymphomas supersede Burkitt/Burkitt-like lymphoma among NHLs. In the present series retinoblastoma totalled six cases, accounting for an incidence of 13.3%. The incidence of this tumor ranges from 1.7 to 38.9% in

Table 3: Distribution of histological tumour types of pediatric solid malignancies in various series

SL. No.	Tumor type	Bannerjee *et al.* (%)	Venugopal *et al.* (%)	Sharma *et al.* (%)	Gupta *et al.* (%)	Sharma *et al.* (%)	Memon *et al.* (%)	Hesham *et al.* (%)	Pandey *et al.* (%)	Present study (%)
1.	Lymphoma	25.9	20.95	21.4	38.3	---	15.9	48.4	31.4	20
2.	Retinoblastoma	8.7	---	6.5	3.3	2.6	38.9	---	5.9	13.3
3.	Soft-tissue sarcoma	14.3	10.4	7.8	8.3	12.2	9.7	5.2	6.5	11.1
4.	Germ cell tumor	3.8	4.8	8.4	11.7	14.5	2.6	---	9.8	11.1
5.	Bone tumor	10.5	3.8	9.7	15	11.9	5.3	4.5	7.2	8.9
6.	Neuroblastoma	4.5	11.4	3.9	3.3	4.9	---	29	4.6	8.9
7.	CNS tumor	15.3	---	9.7	8.3	25.7	10.6	1.9	1.96	6.9
8.	Wilms tumor	8.4	24.8	---	8.3	8.9	13.2	9.7	18.3	4.4
9.	Miscellaneous	8.6	---	20.1	3.3	5.3	7	1.3	5.23	15.6

CNS: Central nervous system

various series, with a study from Pakistan reporting it as the most common pediatric tumor.[6-12,14,17] Nevertheless, retinoblastoma is the most common intraocular childhood malignancy. The frequency of STS as well as the gender predilection in the present series was quite in agreement with the findings of the other series.[10,14,16] Embryonal rhabdomyosarcoma was the most common STS in children. Other series of works such as Prathap *et al.*[27] also have found a similar preponderance of rhabdomyosarcomas [Table 5]. The incidence of malignant GCTs in the present series was 11.1%, which is almost comparable to that of the series of Upadhyay *et al.* and Gupta *et al.*[6,9] All the GCTs were of gonadal origin, whereas Qureshi *et al.* recorded an almost equal distribution at gonadal and extragonadal sites.[15] Neuroblastoma is the most common tumor of early childhood and is rare beyond the age of 10 years. It is a highly aggressive tumor and was reported to have lower incidence among the Indian children by various authors such as Dawani *et al.*, Jussawala *et al.*, and Mangal *et al.*[28-30] Three of the four cases of neuroblastoma in the current study had metastasized to the marrow at the time of presentation. The incidence of marrow involvement ranges from 25.4 to 70% in various series.[31-34] Bone malignancies tend to affect the slightly older children, and the discovery in the present series correlated with that. The authors proclaimed the incidence of these tumors to be 8.9%, while other studies have broadcast it in the range of 3.8–17.9%.[6,9-14,16,17] Similar to other observations, osteosarcoma and ES/PNET were the most common bone malignancies in the current context. The low incidence of CNS in the current study was due to the lack of dedicated neurosurgery services at our center. Nevertheless, in contrast to western studies, the incidence of CNS tumors in Indian studies is less. Medulloblastoma is promulgated as the most common CNS pediatric malignancy. Majority of the Wilms tumors in almost all the series occurred in the first 5 years of life, which was in accordance with the finding in the present study. However, most of the other Indian studies disclosed a higher incidence than ours.[7,10-12,14,17] LCH is an uncommon disease. The annual incidence is about five cases per 1 million population, with most cases occurring in childhood. There is a male predilection, with a male-to-female ratio of 3.7:1.[35] Epithelial malignancies are portrayed by most series in the 10–14 years of age group, a similar reflection as ours. Mucoepidermoid carcinoma is the most common malignant salivary gland tumor in children. Epithelial malignancies adumbrated in other studies besides the ones outlined in ours are follicular thyroid carcinoma, colorectal adenocarcinomas, pancreatic adenocarcinomas, hepatocellular carcinoma, and squamous cell carcinoma of the eye. Among the rarer malignancies perceived in our study were hepatoblastoma, nasopharyngeal carcinoma, and ACC. Hepatoblastoma, though rare, is the most common childhood liver malignancy. Approximately 100 cases are diagnosed yearly in the USA. The most recent SEER data for the period 2002–2008 demonstrates that the highest incidence of hepatoblastoma is in the 0–4 years of age group, with 10.5 and 5.2 cases per million children <1 and 1–4 years.[36] Nasopharyngeal carcinoma has an infrequent incidence rate in children. It rarely appears in children under 14 years of age, and the annual incidence rate in the United Kingdom is 0.25 cases per 1 million inhabitants. It does make up 20–50% of all primary malignant nasopharyngeal tumors in children though.[37] A single case of a rare tumor, ACC was relayed in our study. ACC is a rare neoplasm with an incidence in children of 0.3/million under 15 years of age. They have a bimodal peak; the first one is in the fourth and fifth decades of life and the second one in the first decade, and demonstrate a slight female predilection.[38] Bannerjee *et al.*, and Sharma *et al.* also chronicled ACC in their series.[11,17]

Table 4: Incidence of non-Hodgkin lymphoma and Hodgkin lymphoma in various series

SL. No.	Series	Incidence	
		Non-Hodgkin lymphoma (%)	Hodgkin lymphoma (%)
1.	Pandey *et al.*	13.7	17.6
2.	Gupta *et al.*	11.7	26.7
3.	Hesham *et al.*	31	17.4
4.	Memon *et al.*	2.6	9.7
5.	Present study	15.6	4.4

Table 5: Pattern of soft-tissue sarcomas in various series (in descending order from 1 to 3)

SL. No.	Series	Tumor type		
		1	2	3
1.	Prathap *et al.*	Rhabdomyosarcoma	Fibrosarcoma	Leiomyosarcoma, Liposarcoma
2.	Upadhyay *et al.*	Rhabdomyosarcoma	Fibrosarcoma	Angiosarcoma
3.	Sharma *et al.*	Rhabdomyosarcoma	Synovial sarcoma	
4.	Qureshi *et al.*	Rhabdomyosarcoma	Extraskeletal Ewing sarcoma/PNET	Fibromatosis
5.	Pandey *et al.*	Rhabdomyosarcoma	Malignant fibrous histiocytoma	DFSP
6.	Memon *et al.*	Rhabdomyosarcoma	Fibrosarcoma, Chondrosarcoma	Fibrous histiocytoma
7.	Sharma *et al.*	Extraskeletal Ewing sarcoma/PNET	Rhabdomyosarcoma	---
8.	Present study	Rhabdomyosarcoma	Extraskeletal Ewing sarcoma/PNET, Fibrosarcoma, Synovial sarcoma	---

Accurate diagnosis of pediatric malignancies is important, as disparate approaches to therapy are implemented for distinct tumor types. In addition, therapy is also tailored according to patient risk. The tremendous role of histopathological examination and ancillary studies such as immunohistochemistry, cytogenetic, and molecular analysis in the veracious recognition of the pediatric solid malignancies cannot be understated. The mortality and disability due to cancer can be considerably reduced by early diagnosis and treatment. In order to achieve this, the public health system of the country necessitates country-specific epidemiological data regarding the disease in the population. Moreso understanding the geographic variations in pediatric cancer may contribute to advances in knowledge about etiologic factors.

CONCLUSION

The incidence of childhood solid malignancies observed in this study is not glaringly different from other studies in India and abroad. Neoplasms involving lymphoid tissues, retina, soft tissues, gonads, and bone were among the most common pediatric tumors. Embryonal tumors transpired mainly in the 0–4 year age group, while the >9–14 year age group encompassed mainly of lymphomas, sarcomas, germ cell tumors, and carcinomas. The major limitation of this study was that it was a single institute retrospective analysis conducted during a short span of time with limited number of cases. It was essentially a hospital study which does not claim of the population at large. Yet it was a humble endeavor to assess the incidence and pattern of the dissimilar malignant childhood solid tumors in this part of the country. Cognizance of these patterns and variances will contribute to advances in knowledge about etiologic factors, raise awareness about the global nature of pediatric neoplasms and their histologic distribution and enable public health programs and strategies to be framed using country specific epidemiological data, for early detection and treatment of these deadly pediatric solid malignancies.

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Original Article

To Study the Prevalence of Color Blindness among Adolescent (9th–12th Std.) Schoolchildren in Haldwani

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Abstract

Aims: This study aims to study the prevalence of color blindness among adolescent schoolchildren in Haldwani.

Study Design: A cross-sectional, investigator masked, clinical study was conducted on children.

Place and Duration of Study: This study was conducted at the Department of Ophthalmology Government Medical College Haldwani, Uttarakhand, between June 2018 and June 2020.

Materials and Methods: Students were called according to the roll number in a room. Clinical examinations of both eyes were done. Age and sex of the student were noted. The student was tested for color vision deficiency using Ishihara's type tests for color blindness, 38 plates edition. The color vision testing plates were held at 75 cm from the student and tilted at the right angle to the line of vision. The test was done in adequate lighted room resembling natural day light. Student was asked to read the numbers seen on the test plates and answer was noted down. The time given for telling the number on a plate was <5 s. Assessment of the reading of the plate determines the normality or defectiveness of color vision and also the type of color blindness. It was interpreted as per the instructions given on the booklet provided with Ishihara's type tests for color blindness so as to identify subject suffering from color blindness and also to differentiate the type of color blindness.

Results: The prevalence of color blindness was 202 (3.25%). Deuteranomaly was found among 189 (3.04%) and protanomaly among 11 (0.18%) subjects, deuteranomaly and protanomaly were found among 2 (0.03%) subjects. The prevalence of deuteranomaly was significantly more among males (4.38%) compared to females (1.58%).

Conclusion: This cross-sectional study was done to study the prevalence of color blindness among schoolchildren in Haldwani which included 6212 schoolchildren consisting of 52.2% of males and 47.8% of females. The prevalence of color blindness was found to be 3.25% with deuteranomaly was found among 3.04%, protanomaly among 0.18% of subjects, and combined deuteranomaly and protanomaly were found among 0.03% of subjects.

Key words: Color blindness, Protanomaly-deuteranomaly, Ishihara chart

INTRODUCTION

Color vision is the ability to discriminate a light stimulus as a function of its wavelength. Light with wavelength between approximately 380 and 760 nm causes photoreaction on human retina, which leads to vision. Various sensory and cognitive processes combine to result in the sense of color. Color vision is the capacity to discriminate a light stimulus as a function of its wavelength. Light with wavelength between 380 and 760 nm causes photoreaction on the retina, which leads to visual perception in humans. The sense of color is perceived from the combination of various sensory and cognitive processes.[1,2]

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The description and appreciation of colors depend on the ability of receptors in retina, that is, rods and cones. Rods are mainly responsible for black and white vision, whereas cone systems are mainly responsible for color vision. The Young Helmholtz theory of color vision in human

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postulates the existence of three kinds of cones, each containing a different photo pigment and more sensitive to one of the three primary colors. Only one of the three types of color pigments is present in each of the different cones. The color pigments are called blue-sensitive pigment, green-sensitive pigment, and red-sensitive pigment showing peak absorbencies at light wavelength of 445, 535, and 570 nm, respectively.[3,4] Red, green, and blue are thus called primary colors as any color can be produced by mixing appropriate proportion of red, green, or blue color.[5]

Dyschromatopsia is due to the deficiency of mechanism to perceive color. It has been classified into anomalous trichromatism and dichromatism. Anomalous trichromatism is a form of defective color vision. The terms protanomalous (red), deuteranomalous (green) and tritanomalous (blue) respectively represent the corresponding pigment anomoly.[6]

Dichromatism, the ability to perceive one of three primary colors, is absent. If red color is absent, it is called protanopia. Complete defect for green color is called deuteranopia. In the same way, the absence of blue color is called tritanopia.[7] Cardiovascular disease (CVD) most commonly affects the males, because of recessive trait linked to the X chromosome.[8]

The Ishihara color test is most widely used as the screening test of red-green color deficiency. In Indians, the prevalence was 3.69% in males and 1.04% in females.[9] Among 8–10% of Caucasians, male population was found to affected by red-green color blindness due to congenital protan and deuteran defects.[10]

According to Pease,[11] occupation in the armed forces, aviation, electrical, railways, roadways, and marines has color standard required for employment, while other professions, such as geology, graphic designs, and health-care professions,[12] require normal color vision for effective, efficient, and safe performance. Bacon[13] found that the color differentiation was needed for teaching and learning chemistry, physics, and biology in secondary school. Gordon[14] suggested that CVD affects the activities of children in school, leading to some psychological effect. It is, therefore, important that children know of their color vision status, be advised on how to deal with the condition, and what profession they might choose not to face occupational difficulties.

The Ishihara color test is a test to determine if a patient has color blindness. Hence, it is important to look at the prevalence of color blindness in children and identify the problems associated with it. Keeping the above aspects in mind, the following study has been carried out to find out the prevalence of color blindness in schoolchildren and to make parents and their teachers aware of this disease so that they can modify their teaching methods and choosing and adjusting with suitable profession

MATERIALS AND METHODS

This cross-sectional study entitled "To Study the Prevalence of Color Blindness among Schoolchildren (9^{th}–12^{th}) in Haldwani" was conducted after clearance from Board of Studies and Ethical committee in the Department of Ophthalmology, Dr. Sushila Tiwari Government Hospital, Haldwani, Nainital, during the period of 2018–2020.

Ethical Consideration

Approval from the Institutional Ethical Committee and permission from principal was taken to conduct the study. Informed consent was taken from all the students.

Sample Size

The study population has been calculated using G-power software with 80% of the power and 5% of the significance level. The total sample size was determined to be.

The sample size was calculated using the following formula:
Sample size = 4pq/d2.
P = 8%.
Q= (1−0.08).
D = 20% relative error.
Sample Size = 1150.
Design Effect =2.
1150*2 = 2300.
10% Non-response rate.
Sample size = 2300 + 230 = 2530.
Total schools = 30.

A total of 2530 out of 30 schools by simple random sampling.

Eighty-five students from each school by SRS.

Sample Technique

The sampling technique used was simple random sampling.

Inclusion and Exclusion Criteria

The study subjects were chosen as per the inclusion and exclusion criteria:

Inclusion criteria

1. Healthy students with normal ocular examination findings.
2. Students should be in the age group between 13 and 18 years.
3. Students willing to participate in the study

Exclusion criteria

The following criteria were excluded from the study:

1. Head injury which significantly affects vision.
2. Chronic drug therapy (more than 1 month)
3. Eye diseases.

Study Procedure

After approval from the Institutional Ethical Committee, all patients were selected as per inclusion and exclusion criteria. A detailed history, complete physical examination, and routine and appropriate investigations were done for all patients.

Students were called according to the roll number in a room. Clinical examinations of both eyes were done. Age and sex of the student were noted. The student was tested for color vision deficiency using Ishihara's type tests for color blindness, 38 plates edition.

The color vision testing plates were held at 75 cm from the student and tilted at right angle to the line of vision. The test was done in adequate lighted room resembling natural day light. Student was asked to read the numbers seen on the test plates and answer was noted down. The time given for telling the number on a plate was <5 s.[10] Assessment of the reading of the plate determines the normality or defectiveness of color vision and also the type of color blindness. It was interpreted as per the instructions given on the booklet provided with Ishihara's type tests for color blindness so as to identify subject suffering from color blindness and also to differentiate the type of color blindness.

Early detection of color vision abnormality and its associated problems in children allow parents and teachers to make appropriate adjustment in teaching methods or to take other available measure for the benefit of student. Furthermore, color blind person may found it difficult to work in certain professions which require proper color perception such as traffic policeman, railway driver, and technicians in color industries.

Out of 38 plates, plate numbers 1–25 were used in the present study. The types of color blindness were differentiated with the help of key provided with the chart. According to it, the first plate was presented first to check whether they followed instruction correctly or not. Students who made more than five typical red-green defective responses between plates 2 and 21 were decided to have failed the test.[11,12]

Thereafter, diagnostic plate numbers 22–25 were used to determine the precise type and severity of color vision defects. Those who failed the test were immediately retested and result was noted down in pro forma. List of students suffering from color vision impairment was given to the teachers which they would be asked to inform to respective parents regarding their problem and special care. In this study anomaloscope, the gold standard in color vision test was not used to confirm the diagnosis, further classify the types, and determine the severity of CVD. The instrument was not available in our set up. Of course, the Ishihara test with 38 plate edition has been reported to have high sensitivity and specificity in identifying red-green color vision defects.

Statistical Analysis

The data were entered into the Microsoft Excel and the statistical analysis was performed by statistical software SPSS version 21.0. The quantitative (numerical variables) was present in the form of mean and SD and the qualitative (categorical variables) was present in the form of frequency and percentage.

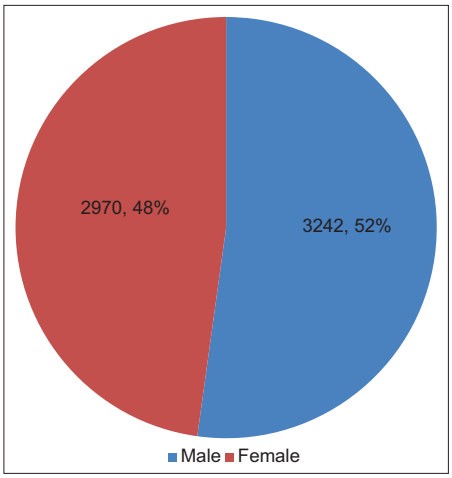
The Student's *t*-test was used for comparing the mean values between the two groups, whereas Chi-square test was applied for comparing the frequency. *P*-value was considered to be significant when <0.05.

RESULTS

Gender

The study population consisted of 3242 (52.2%) males and 2970 (47.8%) females.

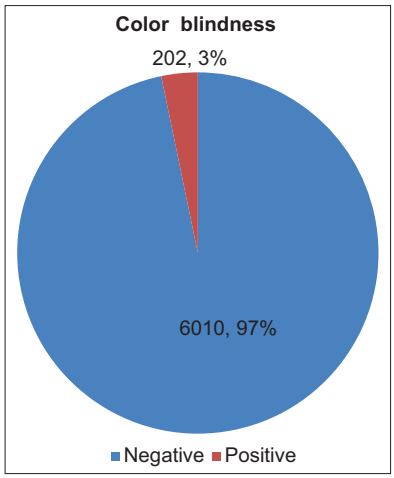
Gender	Frequency	Percent
Male	3242	52.2
Female	2970	47.8
Total	6212	100.0

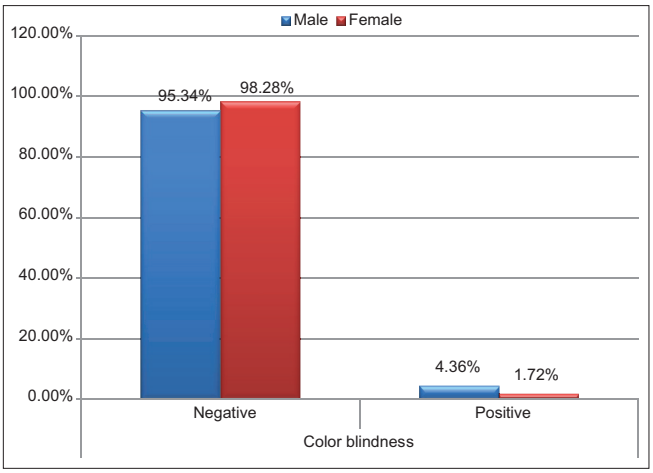


Prevalence of Color Blindness

The prevalence of color blindness was 202 (3.25%).

Color blindness	Frequency	Percent
Negative	6010	96.75
Positive	202	3.25
Total	6212	100.0

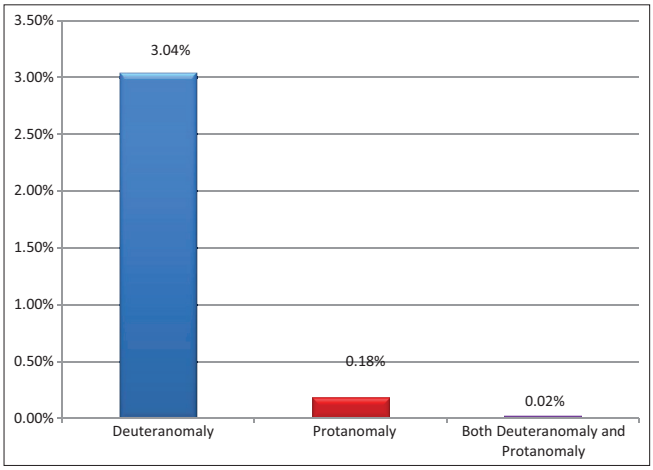




Type of Color Blindness

Deuteranomaly was found among 189 (3.04%) and protanomaly among 11 (0.18%) subjects, deuteranomaly and protanomaly were found among 2 (0.03%) subjects.

	Number	Percentage
Deuteranomaly	189	3.04
Protanomaly	11	0.18
Both deuteranomaly and protanomaly	2	0.03



Prevalence of Deuteranomaly in Genders

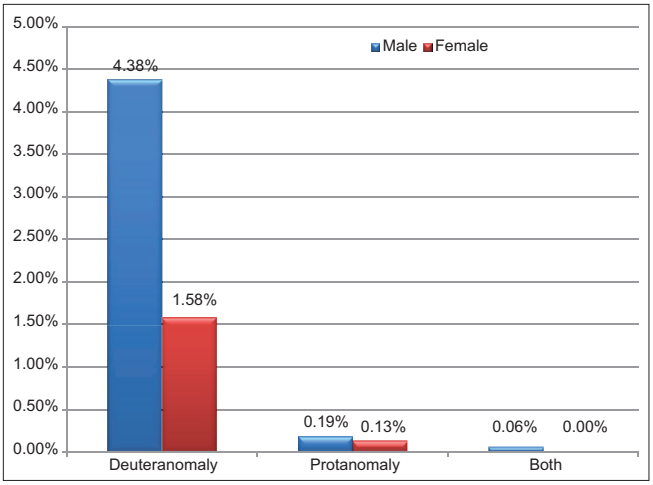
The prevalence of color blindness was compared between males and females using the Chi-square test. The prevalence of color blindness was significantly more among males (4.6%) compared to females (1.7).

	Gender		Total
	Male	Female	
Negative	3091	2919	6010
	95.34%	98.28%	96.75%
Positive	151	51	202
	4.66%	1.72%	3.25%
Total	3242	2970	6212
	100.00%	100.00%	100.00%

χ^2 value=41.911, P<0.001*

The prevalence of deuteranomaly was compared between males and females using the Chi-square test. The prevalence of deuteranomaly was significantly more among males (4.38%) compared to females (1.58%).

	Gender		χ^2 value	*p*-value
	Male	Female		
Deuteranomaly	142	47	37.477	< 0.001*
	4.38%	1.58%		
Protanomaly	7	4	0.579	0.447
	0.19%	0.13%		
Both deuteranomaly and protanomaly	2	0	1.832	0.176
	0.06%	0.00%		



DISCUSSION

This study presents a detailed description of color blindness for the 1st time among male and female primary and high school students in Haldwani, and thus provides the basic epidemiology of color blindness in this region.

Color vision deficiency assessments enable patients to follow the adaptive strategies that could minimize the

risks associated with the disorder. Testing was done using the Richmond Hardy-Rand-Rittler (HRR) test, which is generally considered to be efficient for screening congenital CVD. In addition, the HRR test can reliably detect, categorize, and grade the severity of the protan, deuteran, and tritan color vision deficiencies.[15] The Richmond HRR is, therefore, not only a useful and simple diagnostic device but it also has sufficient sensitivity and specificity to allow investigators to use the results in a clinically meaningful way.[16]

Prevalence

Different prevalence of congenital CVD was reported in literature in different population around the world.[17] In our study, the prevalence of color blindness was found to be 3.2%. This was similar to the studies by Rajkumar *et al*.,[18] the prevalence of color blindness was 3.2% among children aged 10–17 years, Agrawal *et al*.,[19] the prevalence of red-green color deficiency was found to be 3.3%, Wale *et al*.[20] found that the prevalence of color blindness among 850 schoolchildren was found to be 4.24%, Woldeamanuel and Geta,[12] the prevalence of color vision deficiency was 4.1%, which is also nearly similar with the prevalence rates reported in the previous studies.[21] This finding was also comparable with a study done in Thailand, which reported a prevelence of 3.8% among Nigerian male secondary school students studying in Thailand.[22]

Higher prevalence was reported in a study from Singapore,[23] the prevalence of color blindness among Chinese (5.4%), Malay (4.9%), and Indian (4.9%). John *et al*. concluded that the prevalence of CVD in preschool boys varies by ethnicity, with the highest prevalence in non-Hispanic White and lowest in Black children.[24] A higher prevalence of 5.28% was reported in India among Manipuri Muslims of both sexes.[25]

The prevalence of CVD was lower in the study by others be 2.3% reported in Ibadan, Southwest Nigeria, 1.5% found in Zaria, North Nigeria,[26] and 2.6% reported in Port Harcourt, South Nigeria.[14] Ethnically based studies that were conducted in Asia, Europe, and Oceania reported higher prevalence of CVD than the current study, which could be due to racial differences. This suggests that CVD varies among races and geographical regions of the world.

Gender Distribution

In the present study, the prevalence of color blindness was significantly more among males (4.6%) compared to females (1.7%). This coincided with the findings by Woldeamanuel and Geta, the percentage of color vision deficiency was higher among boys (3.6%) as compared to girls (0.6%) and Agarwal and Bansod[27] observed that the prevalence of color blindness among boys was 4.66%. Reddy *et al*. also observed that the prevalence of color blindness in boys was 3.3% in compared to 8% prevalence rate in males among Caucasians in Europe, Great Britain, and the United States,[28] but it is similar to 3–4% prevalence rate of color blindness in the Indian population,[29] 3.3% prevalence rate in male schoolchildren in Guntur.[30] Whereas it is slightly more than the lowest prevelence rate of 2% observed in North America, South America, Fiji and in certain Asian Indian tribes.[31] Wale *et al*.[32] reported that there was a highly significant association between sex and color blindness (adjusted odds ratio = 3.19).

Type of Color Blind Anomaly

In the current study, deuteranomaly was found among 3.04%, protanomaly among 11 (0.18%) subjects, and combined deuteranomaly and protanomaly among 0.03% of subjects. This was in accordance with the study done by Bowmaker,[33] indicated that the most common form of anomalous color vision is deuteranomaly and Woldeamanuel and Geta,[34] most of the color blind children were deuteran. In line with this finding, a high frequency of deuteran as compared to protan defects was observed in other studies.[35] It was suggested that green color receptor is commonly affected than other cone receptors.[36]

The ratio of deuteranopia to protanopia in this study is 2.3:1 as compare to 4.3:1.55 reported by Oriowo[37] and 2.4:0.8 reported by Rajkumar *et al*.[38] The ratio of deuteranopia to protanopia among Saudi in this study is 2.02:0.59 as compare to ratio among non-Saudi 3.23:2.25.

Prevalence of Anomalies among Males and Females

In the current study, the prevalence of deuteranomaly was significantly more among males (4.38%) compared to females (1.58%). Both deuteranomaly and protanomaly were more among males compared to females with no significant difference between them.

This was in accordance with the results by Reddy *et al*., Agarwal and Bansod, there were 11 boys with color blindness include 10 boys with deuteranomaly (i.e., 2.87%) and 1 boy with protanomaly (0.29%). Furthermore, the only girl with color blindness was found to be suffered from deuteranomaly, Moudgil *et al*.[39] on his study among 55 protanopes, 51 were male and 4 were female. Deuteranomaly was observed in six students, of which, four were male and two were female and Shah *et al*.[40] all types of color blind anomalies were more among males than females. It is suggested by several researchers that green color receptor is commonly affected more than red or blue color receptors. This finding is in agreement to several researches.

Color vision is integral to an individual's understanding of their visual world, and those with these defects can experience difficulties in everyday life. However, adaptive strategies and behaviors help to deal with potential difficulties they face in both their professional and personal lives.[41]

In this condition, color blind schoolchildren must be given career advice which includes information as to which career they may find to be difficult or impossible to follow and also help schoolchildren by preventing them from struggling in the classroom due to lack of awareness of the possible effects of their disability by both their parents and teachers. Teachers in the schools must be strictly allowed to give training for the task of color blindness or on how to treat color blind children in a school environment.[42]

Education, screening, and prenatal counseling for the disease in these areas could help a lot in minimizing the occurrence of the disorder and help them to make informed choices and avoid the birth of children with color blindness. Moral support from the family and society is required for the healthy development of mental status of the individual suffering from this disorder. Government should also make certain policies and programs regarding career choices and jobs for color blind individuals.

CONCLUSION

This cross-sectional study was done to study the prevalence of color blindness among schoolchildren in Haldwani which included 6212 schoolchildren consisting of 52.2% of males and 47.8% of females.

The prevalence of color blindness was found to be 3.25% with deuteranomaly which was found among 3.04%, protanomaly among 0.18% of subjects, and combined deuteranomaly and protanomaly were found among 0.03% of subjects.

The prevalence of color blindness was significantly more among males (4.6%) compared to females (1.7%). Furthermore, the different types of anomalies were significantly more among males compared to females.

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Original Article

Comparative Study of Bupivacaine 0.125% with Ropivacaine 0.15% for Post-operative Patient Controlled Epidural Analgesia in Unilateral Total Knee Replacement Surgery in a Prospective, Randomized, Double blinded Study

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Abstract

Background: This study compares a post-operative analgesic efficacy and motor blockade using patient controlled epidural analgesia (PCEA) with either bupivacaine (0.125%) or ropivacaine (0.15%) in unilateral total knee replacement (TKR) surgery by a prospective, randomized, double blinded study in tertiary referral center.

Materials and Methods: Total 60 patients aged 50 years and above, of either sex having ASA Grade I to III, undergone elective unilateral TKR surgery were studied and equally divided into two groups as per randomization. Combined spinal and epidural anesthesia were given at lumbar (L3-4)/(L2-L3) space with 3.1 ml mixture of 0.5% bupivacaine(H) 2.8 ml and 0.3 ml buprenorphine (90 ug) intrathecally. Group A received 0.125% bupivacaine and Group B received 0.15% ropivacaine using a patient controlled analgesia pump epidurally, started ½ h after surgery. Both the groups received these analgesic 5 ml/h for 24 h with initial bolus of 5 ml and demand dose of 5 ml with lock out period of 1 h. Postoperatively, patients were monitored for pain score, sedation score, motor power, and side effect for 24 h.

Results: Pain control is better with Group A (0.125% Bupivacaine). There was statistically significant difference in the mean visual analog scale score and verbal rating scale score in both groups, also requirement of rescue analgesia and additional boluses is more in Group B (0.15% Ropivacaine). There was no statically significant difference in the motor power, sedation score, and side effect.

Conclusion: Epidural 0.125% bupivacaine is superior to 0.15% ropivacaine for post-operative PCEA and comparable in terms of post-operative motor block, sedation score, and side effect.

Key words: Bupivacaine, Patient controlled epidural analgesia, Ropivacaine, Total knee replacement surgery

INTRODUCTION

Joint replacement surgeries are major orthopedic surgeries after spine in the present era. It is not intended to increase quantity of life but to improves mobility and quality of life.[1] Severe post-operative pain is a major complaint in patients who have undergone total knee replacement surgery (TKR). Post-TKR pain directly impacts post-operative physiotherapy and mobilization, which can result in stiffness and poor joint function.[2,3] Effective post-operative pain control is important, especially with the initiation of physiotherapy and early ambulation, which hastens recovery and reduces hospital stay.[4,5] The risk of post-operative complications, such as venous thromboembolism and nosocomial infections,[6] has also been shown to decrease with early mobilization. TKR surgery can be performed under general anesthesia, spinal anesthesia, epidural anesthesia or combined spinal

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epidural (CSE) anesthesia, and under peripheral nerve block.

CSE anesthesia provides not only perioperative surgical anesthesia but extends as post-operative analgesic. Continuous epidural analgesia is becoming popular as an effective method of providing post-operative analgesia. Continuous epidural is more effective and reliable than intermittent injection.[7] The utilization of patient controlled analgesia (PCA) allows patients to complement the analgesia if necessary.[8,9] This innovation, enabling patients to control their own analgesia, improves confidence and reducing the need for nursing care.[10] In this study, only local anesthetic agent either bupivacaine 0.125% or ropivacaine 0.15% is used with PCA pump for post-operative patient controlled epidural analgesia (PCEA) following unilateral TKR surgery in randomized, prospective, and double-blinded clinical study. We are avoiding use of epidural opioids because of their side effect so as to find out the efficacy of local anesthetic agent as well as side effect.

MATERIALS AND METHODS

This study was conducted over a period of 2 years in a tertiary care institute after obtaining approval from the hospital ethical committee and informed consent from all participants. A randomized, prospective, double-blinded clinical study of patients undergoing elective unilateral TKR surgeries receiving continuous epidural infusion of either ropivacaine 0.15% or bupivacaine 0.125% after completion of surgery was undertaken. Sample size was taken as 60 patients, by consecutive type of non-probability sampling method used in selecting study subject during the period of study. All the eligible subject fulfilling the criteria of inclusion/exclusion were taken in study group after prior informed consent. Subjects were divided into two Groups A and B of 30 each by randomization table taken from www.randomization.com. Group A to receive of 0.125% bupivacaine and Group B 0.15% ropivacaine with PCA pump (CADD-LEGANCY® PCA PUMP 6300, Smiths Medical International Ltd, USA, Figures 1 and 2) for post-operative epidural analgesia.

We included adult patients aged 50 years and above of both sexes with ASA Grade I/II/III for the study. All patients were of average height (160–170 cm) and weight (65–75 kg). After pre anesthetic check-up (PAC), patients were kept fasting for past 8 h and premeditated with tablet ranitidine 150 mg and tablet alprazolam 0.25 mg.

Unwilling person, dementia, other mental or psychiatric symptom, hypersensitivity to any of the study drug, anatomical deformity of spine or local infection, patients who need to be converted to general anesthesia and extension of anesthetic duration by giving epidural top ups were excluded from the study.

Patients were explained for pain assessment using visual analog scale (VAS) score and verbal rating scale (VRS) score during pre-operative evaluation. After arrival in OT patient was reassessed and preloaded with IV Ringer's lactate fluid preferably 10 ml/kg body weight. Baseline pulse rate, SpO_2, heart rate, non-invasive blood pressure (NIBP), eletrocardiograph (ECG), and respiratory rate (RR) were noted. Patient was given sitting position, Lignocaine 2% was used for local skin infiltration followed by insertion of 8-cm 18-G Tough epidural needle (Portex, Portex Ltd., Ketn, UK) at lumbar (L3-4)/(L2-L3) interspinous space, under all aseptic precautions. With the help of loss of resistance to air technique, epidural space was located and catheter was inserted 4

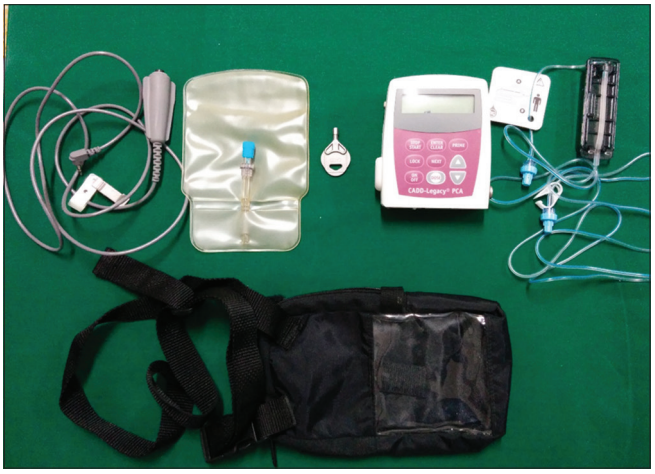

Figure 1: Computerized Ambulatory Drug Delivery [CADD] patient controlled analgesia pump

Figure 2: Patient controlled analgesia pump attached to patients epidural catheter in SICU

cm, confirmed with free flow of fluid. 27G spinal needle was used to give spinal anesthesia with 0.5% bupivacaine heavy (2.8 ml) with 0.3 ml buprenorphine (90 ug). Spinal level was assessed for loss of pinprick sensation to 20 G needle in mid-axillary line. Intraoperatively patients were monitored throughout (Pulse, SpO_2, Heart Rate, NIBP, ECG, Respiratory rate) at 5 min intervals. Any intraoperative complications were assessed and treated accordingly. Duration of tourniquet application was noted.

Postoperatively, patients were observed in recovery room for 30 min and shifted to surgical intensive care unit. Group A received infusion of bupivacaine 0.125% and Group B received infusion of ropivacaine 0.15% with PCA pump epidurally, started 30 min after surgery in anticipation of spinal anesthesia getting worn off. Both the groups received basal continuous epidural infusion at the rate of 5 ml/h for 24 h with initial bolus of 5 ml at the starting of PCA pump. Demand dose is set at 5 ml and taken by patients when feels the breakthrough pain. In between the demand dose, lock-out period of 1 h is kept in which time, though the patient presses demand dose switch, at that time, no drug is delivered. Lock-out period is mainly for patient safety by avoiding excess of drug. Patients were monitored for PR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), RR, SpO_2, sensory level, motor power, sedation score, and side effects every 30 min for first 4 h, thereafter every 4 h till 24 h. Post-operative pain was observed by VAS as subjective score and VRS as objective score. Any fall in SpO_2 below 94% was taken as a respiratory depression. The analgesic solution was prepared by an individual who was not involved in post-operative evaluation. The patients and observer both were blinded for the study. Any post-operative nausea and vomiting were treated with inj Ondansetron 4 mg IV stat. If there was a drop in SpO_2 below 94% for more than 1 min, supplemental oxygen by facemask was administered.

VAS was shown to patients with scale of 0–100 mm, 0 being no pain, and 100 mm being most severe pain. If VAS was above 30 mm then rescue analgesia in the form of injection Diclofenac 75 mg IM was given. VRS was also explained; 0 – no pain, 1 – mild pain, 2 – moderate pain, 3 – severe pain, and 4 – worst. Sedation score assessed as; 1 – awake patients, 2 – mildly sedated easy to wake up (responds to voice), 3 – moderately sedated (responds to tactile stimuli), and 4 – deeply sedated; difficult to wake even to shaking and loud voice. Motor power was assessed by modified BROMAGE scale.

Score	Criteria
1	Complete block (unable to move feet or knees)
2	Almost complete block (able to move feet only)
3	Partial block (just able to move knees)
4	Detectable weakness of hip flexion while supine (full flexion of knees)
5	No detectable weakness of hip flexion while supine
6	Able to perform partial knee bend

Patients were monitored for intraoperative events such as hypotension, bradycardia, respiratory depression, shivering, nausea, and vomiting and followed-up for 24 h for any post-operative complications and appropriately treated.

Other clinical variable noted during study include duration of surgery, total (continuous and PCEA mode) dose of analgesic infused in mg, No. of attempts to take bolus during lockout period, need for supplemental analgesic drugs, level of motor block, and any post-operative complication.

After data collection, data entry was done in Excel. Data analysis is performed with the help of SPSS Software ver 15 and Sigmaplot Ver 11. Quantitative data are presented with the help of Mean, Standard deviation, Median, and comparison among study group is done with the help of Unpaired *t*-test or Mann–Whitney test per results of normality test. Qualitative data are presented with the help of frequency and percentage table, association among study group is assessed with the help of Chi-square test. $P < 0.05$ is taken as significant level.

RESULTS

Both the groups were comparable for demographic variables such as age, gender, height, weight, ASA grading, and duration of surgery [Table 1] so that a random distribution of patients was confirmed to both groups and there were no confounding factors.

There is no statistically significant difference in PR, SBP, DBP, MAP, RR, SpO_2, and sedation score at various time intervals in two groups ($P > 0.05$).

Mean VAS scores in Group A at 1 h, 2 h, 2.5 h, 4 h, 8 h, 12 h, and 20 h were 1.17±0.65, 1.80±1.12, 1.82±1.10, 1.80±0.92,

Table 1: Demographic variable and duration of surgery

Study parameter	Group A	Group B	*P* value
Mean age	63.63±7.81	62.60±6.49	0.453
Sex M/F	14/16	10/20	0.292
Mean height	163.87	160.58	0.093
Mean weight	66.00	68.83	0.173
ASA grading I/II/III	5/18/7	11/13/6	0.209
Mean duration of surgery	80.33	82.23	0.502

2.30±1.51, 2.10±1.03, and 2.07±0.08, respectively. Mean VAS scores in Group B at 1 h, 2 h, 2.5 h, 4 h, 8 h, 12 h, and 20 h were 1.60±0.72, 2.13±0.63, 2.83±1.32, 2.32±1.33, 3.43±1.07, 3.00±0.91, and 2.97±1.22, respectively. VAS score was statistically significant in both groups over 24 h at the above time interval with *P* value for above time intervals respectively are ($P = 0.039$), ($P = 0.015$), ($P = 0.005$), ($P = 0.036$), ($P = 0.013$), ($P = 0.003$), and ($P = 0.001$) [Table 2]. Mean VAS score in Group A at many of the time interval was lower than Mean VAS score in group B, mean pain control is better in Group A than Group B over a period of 24 h.

Mean VRS scores in Group A and Group B at 1 h, 1.5 h, and 2.5 h were 0.87±0.35, 0.97±0.41, 0.93±0.45 and 1.00±0.00, 0.98±0.48, 1.27±0.45, respectively. In our study, VRS scores were statistically significant at many of the time intervals in both groups over 24 h with *P* value at the above time interval are ($P = 0.040$), ($P = 0.049$), and ($P = 0.007$) [Table 3]. It means that pain control is better in Group A than Group B over a period of 24 h.

Motor function in both the groups was statistically significant only a few intervals of time. In Group A mean modified Bromage scale at 1.5 h, 2 h, and 4 h was 1.00±0.00, 1.17±0.38, and 3.67±1.21, respectively. In Group B mean modified Bromage scale at 1.5 h, 2 h, and 4 h was 1.30±0.47, 1.47±0.51, and 4.33±0.66, respectively. *P* value for above time intervals are ($P = 0.040$), ($P = 0.49$), and ($P = 0.007$), respectively [Table 4]. Rest of the time there was no significant difference in motor function in both the groups mostly after 4 h.

Statistically significant difference exists in both groups in terms of total doses of epidural analgesic required (continuous and PCEA mode) (mg) ($P < 0.05$), total

Table 2: Comparison of vas score between bupivacaine group (Group A) and ropivacaine group (Group B)

VAS	Group A			Group B			Mann–Whitney U	P value
	Mean	Std. Dev.	Median	Mean	Std. Dev.	Median		
VAS 0 min (h)	0.00	0.00	0.00	0.00	0.00	0.00	0.000	1.000
0.5	0.30	0.53	0.00	0.40	0.56	0.00	−0.793	0.428
1	1.17	0.65	1.00	1.60	0.72	1.00	−2.064	0.039
1.5	1.57	1.1	1.4	1.77	1.22	1.50	−1.296	0.195
2	1.80	1.21	2.00	2.13	0.63	2.00	−1.954	0.015
2.5	1.82	1.10	2.00	2.83	1.32	3.00	−2.820	0.005
3	2.00	1.05	2.00	2.47	1.50	2.00	−1.111	0.266
3.5	2.27	0.91	2.00	2.27	0.45	2.00	−0.526	0.599
4	1.80	0.92	2.00	2.37	1.33	2.00	−2.092	0.036
8	2.30	1.51	2.00	3.43	1.07	3.00	−3.705	0.013
12	2.10	1.03	2.00	3.00	0.91	3.00	−3.740	0.003
16	2.03	1.00	2.00	2.47	0.73	2.00	−1.852	0.064
20r	2.07	0.87	2.00	2.97	1.22	3.00	−3.187	0.001
VAS 24	1.90	0.80	2.00	2.20	0.89	2.00	−1.151	0.250

"Yellow *P* value denotes statistically significant value." Normality Test (Shapiro–Wilk) failed (*P*<0.05), thus Mann–Whitney rank sum test applied

Table 3: Comparison of verbal rating scale score between bupivacaine group (Group A) and ropivacaine group (Group B)

Verbal rating score (h)	Group A			Group B			Mann–Whitney U	*P* value
	Mean	Std. Dev.	Median	Mean	Std. Dev.	Median		
0	0.00	0.00	0.00	0.00	0.00	0.00	0.000	1.000
0.5	0.27	0.45	0.00	0.37	0.49	0.00	−0.826	0.409
1	0.87	0.35	1.00	1.00	0.00	1.00	−2.053	0.040
1.5	0.90	0.41	1.00	0.98	0.48	1.00	−1.966	0.049
2	0.97	0.41	1.00	1.00	0.00	1.00	−0.463	0.644
2.5	0.93	0.45	1.00	1.27	0.45	1.00	−2.685	0.007
3	0.93	0.37	1.00	1.10	0.40	1.00	−1.656	0.098
3.5	1.03	0.18	1.00	1.00	0.00	1.00	−1.000	0.317
4	0.97	0.41	1.00	1.13	0.35	1.00	−1.644	0.100
8	1.07	0.45	1.00	1.27	0.45	1.00	−1.648	0.099
12	1.07	0.37	1.00	1.13	0.35	1.00	−0.702	0.483
16	0.93	0.37	1.00	1.07	0.25	1.00	−1.619	0.105
20	1.10	0.31	1.00	1.23	0.43	1.00	−1.374	0.169
24	0.97	0.18	1.00	1.03	0.18	1.00	−1.402	0.161

"Yellow *P*value denotes statistically significant value." Normality Test (Shapiro–Wilk) failed (*P*<0.05), thus Mann–Whitney rank sum t applied

dosage of diclofenac required ($P < 0.05$), and no of bolus attempted ($P < 0.05$) [Table 5].

DISCUSSION

TKR is a common orthopedic surgery generally performed in elderly patients to relieve morbidity associated with osteoarthritis and other related joint disorders. After surgery, pain relief is essential to enable ambulation and initiate physiotherapy, but post-operative pain management can be influenced at an institutional level by factors such as local experience, skills (particularly for regional techniques) and practice.

CSE anesthesia is safer in the elderly unless absolutely contraindicated and remains a useful anesthetic technique for lower limb arthroplasty. It combines the advantages of both spinal and epidural technique by initially providing an intense blockade of rapid onset, later post-operative pain relief. So the technique of CSE anesthesia was chosen.[11,12]

In our study, continuous epidural infusion was used using PCEA for post-operative pain and provides superior pain control, allows the patient to undertake physiotherapy thus adding the better outcome of surgery with shorter recovery time. Continuous epidural is specifically suited for TKR as patient is not ambulated after wearing off anesthesia 24 h postoperatively.[13] This stage of immobility if associated with severe pain can cause significant morbidity in the form of venous thromboembolism. During PCEA, patient controls the administration of analgesic according to severity of pain. PCEA system allows on-demand bolus injections with the option of a background infusion. Over dosage is avoided by limiting the size of the bolus and setting a lock-out interval between two doses.

Epidural infusion of local anesthetics is one of the most effective ways of post-operative pain relief,[14,15] also promote reconvalescence by blunting autonomic and somatic reflexes to pain.[16,17] We used the local anesthetic in the lower concentration without opioids to know their analgesic efficacy, as a new tool in the postoperative pain management. As well, we could not find many references of study of 0.15% ropivacaine concentration for post-operative analgesia.

In our study with respect to demographic variables as age, gender, height, weight, ASA grading, and mean duration of surgery, both the groups were comparable and statistically not significant so it does not alter and keeps the uniformity in post-operative analgesia management.

Table 4: Comparison of motor function between bupivacaine group (Group A) and ropivacaine group (Group B)

Motor function	Group A			Group B			Mann–Whitney U	*P* Value
	Mean	Std. Dev.	Median	Mean	Std. Dev.	Median		
Motor function 0 (h)	1.00	0.00	1.00	1.00	0.00	1.00	0.000	1.000
0.5	1.00	0.00	1.00	1.00	0.00	1.00	0.000	1.000
1	1.00	0.00	1.00	1.00	0.00	1.00	0.000	1.000
1.5	1.00	0.00	1.00	1.30	0.47	1.00	−3.227	0.001
2	1.17	0.38	1.00	1.47	0.51	1.00	−2.477	0.013
2.5	1.83	0.75	2.00	2.03	0.56	2.00	−1.234	0.217
3	2.53	1.25	2.50	2.77	0.68	3.00	−0.984	0.325
3.5	3.07	1.28	3.00	3.57	0.68	3.00	−1.682	0.093
4	3.67	1.21	4.00	4.33	0.66	4.00	−2.186	0.029
8	4.33	0.92	5.00	4.67	0.48	5.00	−1.204	0.228
12	4.73	0.58	5.00	4.83	0.38	5.00	−0.440	0.660
16	4.87	0.43	5.00	4.87	0.35	5.00	−0.345	0.730
20	4.97	0.18	5.00	5.00	0.00	5.00	−1.000	0.317
24	4.99	0.19	5.00	5.00	0.01	5.00	−1.000	0.318

"Yellow *P* value denotes statistically significant value." Normality test (Shapiro–Wilk) failed (*P*<0.05), thus Mann–Whitney rank sum test applied

Table 5: Comparison of drugs associated variable in two group

Study Parameter	Group A			Group B			Unpaired *t* test	*P* Value
	Mean	Std. Dev.	Median	Mean	Std. Dev.	Median		
Total mg of analgesia required* (continuous and PCEA)	168.88	42.59	178.63	226.75	11.60	225.00	−6.687	0.002
No of bolus attempted*	1.67	1.09	2.00	4.00	1.58	4.00	−5.408	0.03
Total dosage of diclofenac required*	0.67	0.80	0.50	1.67	0.84	1.00	−3.696	0.012

"yellow *P* value denotes statistically significant value." *P* value calculated for Unpaired T test except at "*." "*" Normality test (Shapiro-Wilk) Failed (*P*<0.050), thus *P* value calculated for Mann–Whitney rank sum test

PR, SBP, DBP, MAP, RR, SpO_2, and sedation score were comparable in both the groups at any of the time intervals over 24 h ($P > 0.05$). These findings were supported by study conducted by Hoka *et al.,* [18] in which patients undergoing ipsilateral leg orthopedic surgery with epidural or CSE anesthesia were randomly assigned to three groups: 0.1% ropivacaine; 0.2% ropivacaine; and 0.125% bupivacaine. At the end of surgery, continuous epidural infusion was started at a rate of 6 ml/h after a bolus epidural administration of 5 ml. Vital signs were stable at every measuring point in all the groups.

VAS Score was the primary outcome that was compared. Mean VAS scores in Group A and Group B at time interval of 1 h, 2 h, 2.5 h, 4 h, 8 h, 12 h, and 20 h were 1.17±0.65, 1.80±1.12, 1.82±1.10, 1.80±0.92, 2.30±1.51, 2.10±1.03, and 2.07±0.08 and 1.60±0.72, 2.13±0.63, 2.83±1.32, 2.32±1.33, 3.43±1.07, 3.00±0.91, and 2.97±1.22, respectively, in both group. Mean VAS was statistically significantly different at many of the time intervals in both the groups over 24 h with *P* value for above time intervals, respectively, are ($P = 0.039$), ($P = 0.015$), ($P = 0.005$), ($P = 0.036$), ($P = 0.01$), ($P = 0.003$), and ($P = 0.001$). Mean VAS score in Group A at many of the time intervals is lower than Mean VAS score in Group B; it means pain control is better in Group A.

In study conducted by Muldoon *et al.*,[19] compared the analgesia and motor block produced by extradural infusions of ropivacaine 0.2% or bupivacaine 0.2% after TKR in Fifty-two patients at 8 ml/h for 24 h after operation. Analgesia was assessed by post-operative VAS and morphine consumption. VAS score was more in ropivacaine group with more morphine consumption as compared to bupivacaine group.

In our study, pain score is lower in bupivacaine group (0.125%) than ropivacaine group (0.15%).

Mean VRS scores in Group A and Group B at 1 h, 1.5 h, and 2.5 h was 0.87±0.35, 0.97±0.41, and 0.93±0.45 and 1.00±0.00, 0.98±0.48, and 1.27±0.45, respectively, in both the group. VRS scores were statistically significant in Group A and Group B over 24 h with *P* value at the above time interval are ($P = 0.040$), ($P = 0.049$), and ($P = 0.007$), shown pain control is better in Group A.

Total doses of local anesthetic required (continuous and PCEA mode) (mg) in Group A and Group B were 168.88±42.59 mg and 226.75±11.60 mg, respectively, and statistically significant ($P = 0.002$).

Heid *et al.*[20] evaluated the analgesic efficacy of epidural ropivacaine 0.2% versus bupivacaine 0.125% after retropubic prostatectomy in 40 patients by patient-controlled lumbar epidural analgesia and shows ropivacaine consumption are 60% higher than that of bupivacaine ($P < 0.001$).

Intramuscular diclofenac is given to the patient as a supplementary analgesia if their VAS score exceeded >30 mm, maximum dose is limited to three doses of 75 mg of diclofenac in 24 h, two doses were kept at least 4 h apart. In our study group, requirement of diclofenac was statistically significant ($P = 0.012$) as it is 0.67±0.80 doses in Group A and 1.67±0.84 doses in Group B.

Muldoon *et al.*[19] showed that median morphine consumption was 30.7 mg in the ropivacaine group and 20.5 mg in the bupivacaine group. They used additional analgesia of morphine by iv PCA and in our study we used inj diclofenac 75 mg by im route. In both the studies, requirement is more with ropivacaine group.

Furthermore, in Group A mean number of attempted boluses was 1.67±1.09 and in Group B 4.00±1.58, significantly differ as $P = 0.03$. It shows that there is better analgesic control with bupivacaine rather than ropivacaine.

Thus, all above finding proving epidural bupivacaine 5 ml/h (6.25 mg/h) of 0.125% to be superior to epidural ropivacaine 5 ml/h (7.5 mg/h) of 0.15%.

The secondary objective compared is the motor function score for the two groups. Motor function in ropivacaine group was better in first 4 h, then both the groups were comparable and statistically not significant up to 24 h period ($P = 0.321$). Korula *et al.*[21] conducted study to compare the clinical efficacy of ropivacaine 0.2% and bupivacaine 0.125% for post-operative analgesia in patients undergoing bilateral mesh hernioplasty. Motor block achieved with bupivacaine was of greater intensity in the beginning but after 30 min, difference was not significant and duration of motor block was similar in two groups. This supports our finding.

In both the groups, incidence of hypotension, nausea, and vomiting was comparable and statistically not significant. Out of total 60 patients, only one patient had complained of pruritus in Group B which was statistically insignificant. Respiratory depression is always associated with deeper sedation which was not seen in any of the patient in our study. The changes in respiratory rate were also not statistically significant.

CONCLUSION

We concluded that epidural 0.125% bupivacaine (6.25 mg/h) is superior to 0.15% ropivacaine (7.5 mg/h)

for post-operative PCEA. Post-operative motor function was better in first 4 h in terms of Bromage score with ropivacaine following unilateral TKR surgery. None of the groups showed any hypotension and respiratory system related side effect at this low concentration.

Limitation

In our study, as the concentration used for ropivacaine was 0.15%, we did not get enough references for each and every parameter for comparison. Larger study need to be conducted to confirm these findings.

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Original Article

Association of Low Pregnancy-associated Plasma Protein-A Level in Late First Trimester with Various Pregnancy Complications

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Abstract

Aim and Objective: This study aims to see association of low pregnancy-associated plasma protein-A **(**PAPP-A) level in late first trimester (10–13 weeks) with various pregnancy complications.

Materials and Methods: Pregnant women (*n* = 491) at 11–13 weeks of gestation were recruited from antenatal clinic after confirmation of fetal viability. Two milliliters of blood sample were collected and serum PAPP-A level was measured.

Results: Out of 491, 461 followed till term. During course of follow-up, adverse pregnancy outcome noted in 117 (25.3%) subjects, as small for gestational age (SGA) in 10.8%, preterm labor in 4.7%, preeclampsia in 4.6%, premature rupture of membrane (PROM) in 2.4%, abruption in 1.5%, and intrauterine fetal death (IUFD) in 1.3%. The median (IQR) PAPP-AMOM for preterm labor 0.50 (0.42–0.63), PROM 0.45 (0.23–0.59), preeclampsia 0.27 (0.19–0.39), abruption 0.30 (0.08–2.05), intrauterine demise was 0.166 (0.078–0.389), and SGA 0.62 (0.26–0.74). The median (IQR) PAPP-AMOM for pregnancy without any complication was 2.12 (0.8–5.03). The median PAPP-AMOM value was significantly lower ($P < 0.05$) in cases of SGA, preterm labor, preeclampsia, PROM, abruption, and IUFD in comparison to normal pregnancy.

Conclusion: Low serum PAPP-A levels from in late 1st trimester are a good predictive marker of various pregnancy complications.

Key words: Defective implantation, Intrauterine fetal death, Preeclampsia, Pregnancy-associated plasma protein-A, Small for gestational age

INTRODUCTION

Pregnancy-associated plasma protein-A (PAPP-A) is a glycoprotein and produced by syncytiotrophoblast and decidual cells and detected in maternal serum, placental tissue, and amniotic fluid and coelomic fluid.[1] It is a Zn metalloproteinase with an elongated Zn-binding motif which has been identified as insulin-like growth factor-binding protein-4 proteinase that increase bioavailability of insulin-like growth factor 1 and 2. At maternal fetal interface, insulin-like growth factor 2 (IGF-2) bioavailability mediated by PAPP-A enables trophoblast invasion into maternal decidua, steroidogenesis, and glucose and amino acid transport into chorionic villous cytotrophoblast.[2] Literature suggest that inadequate trophoblast invasion is risk factor for various adverse pregnancy outcomes.

Maternal serum PAPP-A along with beta-hCG and nuchal translucency widely used as marker of aneuploidy in the 1st trimester. The low levels of PAPP-A are associated with adverse pregnancy outcomes. Similar test can be used for prediction for various pregnancy complications along with aneuploidy. Thus, the current study planned to see association of low 1st trimester PAPP-A levels with various pregnancy complications such as preeclampsia, fetal growth restriction, preterm, abruption, and intrauterine fetal death (IUFD) in Indian population.

PAPP-A starts appearing in maternal serum after the 5th week of pregnancy and its levels continue to increase with

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time. PAPP-A level increases exponentially with doubling time of 3–4 days during the 1st trimester of pregnancy. Peak levels of PAPP-A are observed at the end of pregnancy and levels are downregulated subsequently at delivery.[1]

Various factors affect maternal serum PAPP-A level like gestational age and maternal characteristics including weight, racial origin, cigarette smoking, diabetes mellitus, and method of conception. PAPP-A level is more in twin pregnancy.[3,4]

MATERIALS AND METHODS

This was an observational, cross-sectional study conducted in the Department of Obstetrics and Gynecology in collaboration with the Department of Biochemistry at University College of Medical Sciences and Guru Teg Bahadur Hospital, Delhi, from November 2016 to April 2018. Pregnant women presenting to the outpatient department of obstetrics and gynecology were recruited on the basis of inclusion criteria such as spontaneously conceived, ultrasound confirmed intrauterine singleton pregnancy at 10–13 weeks of gestation with maternal age between 20 and 30 years, and normal body mass index (BMI). They were excluded from study if history of medical disorders such as diabetes mellitus, hypertension, asthma, antiphospholipid syndrome, thyroid dysfunction, liver and renal disease, and history of smoking present. Pregnancy with anomalous fetus detected during follow-up and women unwilling to participate were excluded from the study.

A total of 491 pregnant women were enrolled from antenatal OPD on the basis of inclusion criteria at 10–13 weeks of gestation. Ethical clearance was obtained from Institutional Ethical Clearance Committee for human research. An informed written consent was taken from all the subjects after enrollment. Confirmation of gestational age was done on the basis of definite last menstrual period (with 3 previous cycle regular) and first trimester ultrasonography (using CRL).

All cases enrolled were interviewed to collect information on age, address, occupation, religion, education, socioeconomic status, substance abuse, trauma, family history of genetic anomaly, etc., in a properly designed questionnaire.

Two milliliters of peripheral blood sample in plain vial were collected at the time of enrollment along with routine antenatal investigation, clotted sample was centrifuged at 3000 rpm for 15 min, and separated serum was stored at −20°C in the department of biochemistry for analysis of PAPP-A level in all subjects. All pregnant women were followed till term to observe various pregnancy outcomes.

Serum samples of all subjects were evaluated for PAPP-A levels by PAPP-A ELISA Kit (DRG International, Inc., USA) which was based on solid phase enzyme-linked immunosorbent assay (sandwich ELISA). Microsoft Excel (version 2013) and statistical software SPSS for Windows (version20.0) were used for data presentation and statistical analysis. PAPP-A levels were calculated in multiple of median (MOM). Independent t-test and Chi-square test were applied to compare continuous data that are normally distributed such as age, BMI, and sociodemographic profile. Mann-Whitney *U*-test to compare data that was not normally distributed like PAPP-A MOM.

RESULTS

We had followed 461 out of 491 pregnant women till term pregnancy to observe various other pregnancy outcomes. Thirty women lost to follow up. Out of 461 subjects, 27 had spontaneous abortion before 20 weeks and 117 women developed complication such as preterm delivery, small for gestational age (SGA), abruption, preeclampsia, and IUFD. Rest of 317 delivered without any complications. PAPP-AMOM of various adverse pregnancy outcomes was compared with PAPP-AMOM of normal pregnancy outcome.

Study population largely comprised females between 20 and 24 years of age (61.1%) followed by between 25 and 29 years of age (33%) and majority of study subjects were Hindu by religion (77.4%) and 22.6% were Muslim. Mean age of the study population was 24.08±2.92. Most of the subjects in the study population belonged to either lower middle (42.6%) or upper lower (40.1%) socioeconomic status. Most of the study subjects were educated (96.6%). Most of them were

Table 1: Sociodemographic characteristics of the study population

Characteristics	Study population (*n*=491) *n* (%)
Age (years) mean	24.08±2.92
20–24	300 (61.1)
25–29	162 (33)
30–34	29 (5.9)
Religion	
Hindu	380 (77.4)
Muslim	111 (22.6)
Socioeconomic status*	
Upper	3 (0.6)
Upper middle	80 (16.3)
Lower middle	209 (42.6)
Upper lower	197 (40.1)
Lower	2 (0.4)
Education	
Illiterate	17 (3.4)
Primary/middle	156 (31.8)
High	211 (43)
Intermediate	57 (11.6)
Graduate/professional	50 (10.2)

*Modified Kuppuswamy's socioeconomic status scale

housewife [Table 1]. The mean BMI of the study population was 21.58±1.69 kg/m^2 [Table 2]. Most of women in the study population were primigravida (45.6%) followed by 2nd gravida (37.7%) and 16.7% were 3rd and more gravida [Table 3].

During course of follow-up, adverse pregnancy outcome noted in 117 (25.3%) subjects, as SGA in 10.8%, preterm labor in 4.7%, preeclampsia in 4.6%, premature rupture of membrane (PROM) in 2.4%, abruption in 1.5%, and IUFD in 1.3% [Table 4].

The median (IQR) PAPP-AMOM for preterm labor 0.50 (0.42–0.63), PROM 0.45 (0.23–0.59), preeclampsia 0.27 (0.19–0.39), abruption 0.30 (0.08–2.05), intrauterine demise was 0.166 (0.078–0.389), and SGA 0.62 (0.26–0.74). The median (IQR) PAPP-AMOM for pregnancy without any complication was 2.12 (0.85–5.03). The median PAPP-AMOM value was significantly lower ($P < 0.05$) in cases of SGA, preterm labor, preeclampsia, PROM, abruption, and IUFD in comparison to normal pregnancy [Table 5]. Hence, low PAPP-AMOM value is a very good predictive marker for various adverse pregnancy outcomes.

Table 2: Maternal body mass index at time of enrolment in the study population

Body mass index (kg/m^2)	Study population (*n*=491)
(Mean)	21.58±1.69
18.5–22.5	358 (72.9%)
22.6–24.9	133 (27.1%)

Table 3: Distribution of parity in the study population

Parity	*n* (%)
Primigravida	224 (45.6%)
2nd gravida	185 (37.7%)
3rd gravida or more	82 (16.7%)

Table 4: Incidence of various pregnancy outcomes in the study population (*n*=461) as described above

Pregnancy outcome group	*n* (%)
Miscarriage	27 (5.9)
Preterm labor	22 (4.7)
Premature rupture of membrane (PROM)	11 (2.4)
Preeclampsia	21 (4.6)
Abruption	7 (1.5)
Intra uterine fetal death	6 (1.3)
Small for gestational age	50 (10.8)
Normal pregnancy	317 (68.8)

DISCUSSION

The mechanism involved in most of adverse pregnancy outcome is same as that of miscarriage. Decreased PAPP-A levels leading to decrease free IGF levels which possibly leads to diminished fetal growth, placental growth and abnormal placentation. This is the main pathophysiology of adverse pregnancy outcome such as SGA, preeclampsia, preterm, PROM, abruption, and IUFD.

In our study, subjects were comparable in respect to sociodemographic profile, parity, and BMI. We found that median PAPP-AMOM value was significantly lower ($P < 0.05$) in cases of SGA, preterm labor, preeclampsia, PROM, abruption, and IUFD in comparison to normal pregnancy. These findings were in consensus with the study of Barrett *et al.*, Dugoff *et al.*, Cohen *et al.*, and Krantz *et al.*[5-8]

Patil *et al.*[9] recruited 524 subjects at 11–13 weeks of gestation for the 1st trimester fetal surveillance who registered for delivery in their hospital. They defined low PAPP-A cutoff <0.5 MOM and observed that significant rise in incidence of preterm labor, fetal growth restriction, and preeclampsia with low PAPP-A levels in the 1st trimester. They did not calculate median PAPP-AMOM value in respective adverse outcome group. Gupta *et al.*[10] also noted incidence of adverse pregnancy outcome in subjects whose PAPP-AMOM levels ≤0.4 MOM and >0.4 MOM. They observed that incidence of FGR ($P = 0.001$), preterm delivery ($P = 0.046$), low birth weight ($P = 0.0001$), but statistically no difference in preeclampsia ($P = 0.075$), and with abruption (0.394).

Table 5: Comparison of median (IQR) of PAPP-AMOM value of adverse pregnancy outcome group with normal pregnancy outcome group

Pregnancy outcome	Median (IQR) of adverse pregnancy outcomes	Median (IQR) of normal pregnancy	*P value
Preterm labor (*n*=22)	0.50 (0.42–0.63)	2.12 (0.85–5.03)	0.001
Premature rupture of membranes (*n*=11) Premature rupture of membrane (PROM)	0.45(0.23–0.59)	2.12 (0.85–5.03)	0.001
Preeclampsia (*n*=21)	0.27 (0.19–0.39)	2.12 (0.85–5.03)	0.001
Abruption (*n*=7)	0.30 (0.08–2.05)	2.12 (0.85–5.03)	0.036
Intrauterine fetal death (*n*=6)	0.166 (0.078–0.389)	2.12 (0.85–5.03)	0.001
Small for gestational age (*n*=50)	0.62 (0.26–0.74)	2.12 (0.85–5.03)	0.001

*P<0.05 was considered significant, Mann–Whitney U-test

Low PAPP-A levels may be indictor of impaired placental function and implantation and this may be explanation for the association of low PAPP-A levels and subsequent development of adverse pregnancy outcome including preeclampsia, SGA, preterm, abruption, and IUFD.

First trimester low PAPP-A levels can be used to classify patients as high risk or low risk for some adverse pregnancy outcome apart from Down syndrome screening. It helps clinician in the management of high-risk pregnancy, early initiation of treatment, and prognostication of patient.

The study was limited by small number of study population. Analysis of PAPP-A level in large population was not possible because of time and financial constraints.

CONCLUSION

Low PAPP-A level at late first trimester is associated with various pregnancy complications. It may be useful tool for assessing risk of adverse fetal outcome in high-risk pregnancy or in combination of other test.

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Original Article

A Comparative Study on Prevalence and Severity of Hypothyroidism among Women with Preeclampsia

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Abstract

Introduction: Thyroid dysfunction is one of the most common endocrine disorders encountered during pregnancy after diabetes mellitus. Pregnancy develops significant changes in hypothalamic-pituitary-thyroid axis, iodine metabolism, and the immune function. Thyroid physiology alters to meet increased metabolic demands in pregnancy.

Aim: The aim of this study was to compare the prevalence and severity of hypothyroidism among women with preeclampsia and normotensive patients.

Materials and Methods: This is a hospital-based observational case–control study. A total of 200 women are included, out of them 100 normal pregnant women in the control group and 100 preeclamptic women in the case group are included in this study. Informed consent was obtained from the patients. The results are statistically analyzed and discussed below.

Results: Out of 200 subjects, the patients' mean age in control group and study groups was 28.07 ± 4.89 and 24.42 ± 4.93 years. In study group out of 100 patients, 70 had a euthyroid state, 28 had subclinical thyroid state, and two patients had overt thyroid. In the control group out of 100 patients, 86 had a euthyroid state, 11 had subclinical thyroid, and three patients had overt thyroid. Mean value of TSH in the study group is higher compared to the control group. Mean value of FT4 in the study group is less compared to the control group.

Conclusion: We concluded that the preeclampsia had a higher incidence of hypothyroidism (SCH) in contrast to the normotensive women, and there is a correlation between the severity of preeclampsia and hypothyroidism.

Key words: Hypothyroidism, Preeclampsia, Pregnancy, Thyroid

INTRODUCTION

Thyroid dysfunction is one of the most common endocrine disorders encountered during pregnancy after diabetes mellitus. It has long been recognized that maternal thyroid hormone excess or deficiency can influence the outcome for mother and fetus and interfere with ovulation and fertility.[1,2] The prevalence of hypothyroidism in pregnancy is around 2.5% according to the western literature. There are few reports of hypothyroidism during pregnancy from India with rates ranging from 4.8% to 11%.[3,4] Pregnancy develops significant changes in hypothalamic-pituitary-thyroid axis, iodine metabolism, and the immune function. Thyroid physiology alters to meet increased metabolic demands in pregnancy. There is estrogen stimulation which increases the circulating levels of thyroid-binding globulin. The proposed mechanism is increased excretion of the iodine secondary to fetal intake and placenta metabolism, leading to a decline in iodine availability. Total concentrations of thyroxine (T4) and triiodothyronine (T3) increase in the first trimester of pregnancy achieving the plateau early in the second trimester, followed by reaching concentration 30–100% greater than the pre-pregnancy levels after the rise in thyroid-binding globulin.

Thyroglobulin increases during pregnancy secondary to the enhanced activity of the thyroid gland. Hypothyroidism in pregnancy complicates pregnancy through various mechanisms. It increases the risk of preeclampsia. Studies have found that women with hypothyroidism during

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pregnancy have an increased risk of preterm labor and instrumental deliveries. They were found to have increased abortion, intrauterine death as compared to women with normal functioning thyroid.

Hypothyroidism has been observed as one of the causes of high blood pressure. There is the failure of estrogen production and placental dysfunction in preeclampsia, resulting in low TBG, TT3, and TT4. Experimental studies have indicated that release of NO is altered in hypothyroidism and the resulting endothelial cell dysfunction might be a pathogenetic mechanism for hypothyroidism in preeclampsia.

Thyroid dysfunction during pregnancy is associated with adverse maternal complications such as miscarriages, anemia complicating pregnancy, preeclampsia, abruptio-placentae, postpartum hemorrhage, and fetal complications such as premature birth, low-birth weight, and increased neonatal respiratory distress. Maternal and fetal hypothyroidism can also result in irreversible brain damage with mental retardation and neurologic abnormalities which justifies screening for thyroid dysfunction during early pregnancy with interventional levothyroxine therapy for thyroid hypofunction.[5-10]

Aim

The aim of this study was to compare the prevalence and severity of hypothyroidism among women with preeclampsia and normotensive patients.

MATERIALS AND METHODS

This is a hospital-based observational case–control study. A total of 200 women are included, out of the 100 normal pregnant women in the control group, and 100 preeclamptics women in the case group. The patients were classified as euthyroid, subclinical hypothyroid, overt hypothyroid, and hyperthyroid based on their TSH levels and T4 testing. Inclusion criteria in the case group include pregnant women >37 weeks' gestation, a diagnosed case of preeclampsia, previously normotensive, and in the control group, including pregnant women >37 weeks and normotensive. Exclusion criteria include previous H/O medical renal and hepatic disease, hyperthyroidism and endocrine disorders, RHD, not on any chronic drugs, multiple gestation, and molar pregnancy.

10 mL venous blood to be drawn for thyroid hormone analysis (FT3, FT4, and TSH) using chemiluminescent assay. Particulars of the women are noted, such as name, age, symptoms, menstrual history for menarche, last menstrual period and past menstrual cycles, and history of present pregnancy. Obstetric history to be asked for marriage duration, infertility, gravida and parity status, recurrent abortions, preeclampsia, growth restriction, low birth weight, preterm delivery, prematurity, late losses, neonatal deaths, and mental retardation in a previous pregnancy.

Medical history was asked for any associated medical disorders such as diabetes, thyroid disorders, exposure to radiation, or autoimmune disorders. Significant surgical history, family history was also asked. A thorough clinical examination, including height, weight, pulse, blood pressure, pedal edema, and thyroid enlargement, was done by systemic examination. In an obstetrical examination, presentation and liquor were noted, and fetal heart sounds were auscultated.

All preliminary and baseline investigations such as complete blood count, blood grouping and typing, urine routine and microscopy, and blood sugar were done. Ultrasonography was done for fetal growth, liquor, and placenta. All investigations about preeclampsia complications such as liver and kidney function tests and serum uric acid were also done.

RESULTS

Out of 200 subjects, the patients' mean age in control and study groups was 28.07 ± 4.89 and 24.42 ± 4.93 years ($P = 0.35$) [Figure 1].

In the study group, out of 100 patients, 70 had a euthyroid state, 28 had subclinical thyroid state, and two patients had overt thyroid. In the control group, out of 100 patients, 86 had a euthyroid state, 11 had subclinical thyroid, and three patients had overt thyroid [Figure 2].

Mean value of TSH in the study group is higher compared to the control group. Mean value of FT4 in the study group is less compared to the control group [Figure 3].

DISCUSSION

The age distribution of patients included in our study ranged from 18 to 40 years. Majority of them belonged to the <21–30 years in both the groups. The patients' mean age in the control and study group was 28.07 ± 4.89 and 24.42 ± 4.93 years, respectively, which was comparable ($P = 0.35$).

In a similar study done by Ashokkumar *et al.*,[11] comparing preeclampsia with normotensive women, the mean (SD) age of the study group and the control group was 28.4 ± 6.24 years and 27.5 ± 5.91 years, respectively, which is quite similar to our study.

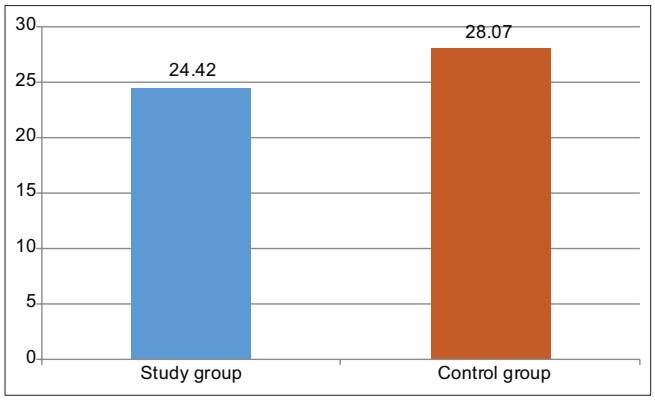

Figure 1: Age distribution

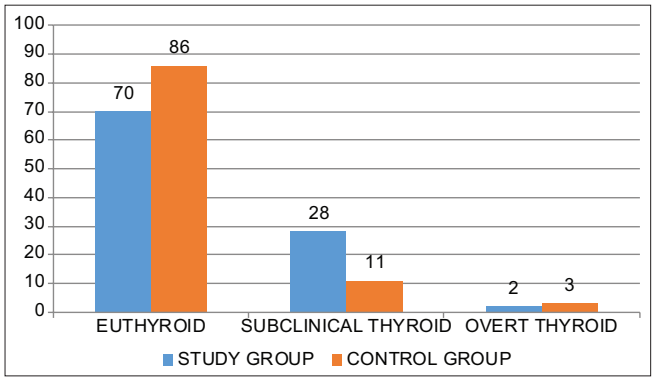

Figure 2: Type of thyroid state

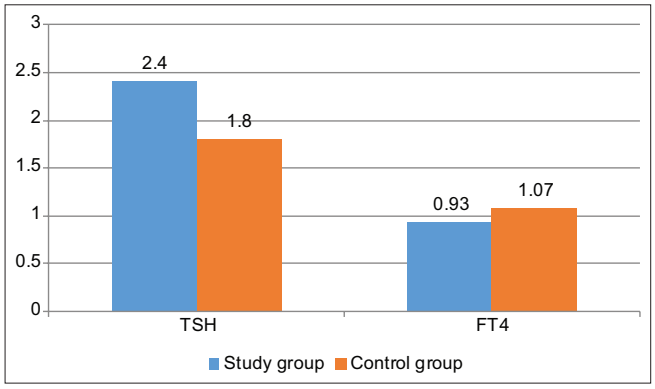

Figure 3: Thyroid function test

TSH, free T4 was done for both the groups and the results were analyzed. The control group in our study had 86 euthyroid subjects (86%), 11 subclinical hypothyroid (11%), and three overt hypothyroid (3%).

In the preeclampsia group, 70 were euthyroid (70%), 28 are subclinical hypothyroid (28%), and two are overt hypothyroid (2%). These findings follow the previous literature stating that preeclampsia women have a higher incidence and prevalence of biochemical hypothyroidism than the normotensive population.[12-15]

The mean TSH value in the preeclampsia group is more than the controls in our study (2.4 ± 1.3 vs. 1.8 ± 0.9). It is significant. Our study's mean free T4 values in preeclampsia versus controls is 0.93 ± 0.28 versus 1.07 ± 0.33, which remains within the normal trimester-specific range of FT4. However, the PE group had a mean FT4 level lower than the controls and the difference was statistically significant ($P < 0.0001$).

Thus, subclinical hypothyroidism is more common in the preeclampsia group in the present study and is similar to the study done by Kumar *et al.*,[11] the mean FT4 is not significantly different in the two groups and the mean TSH value was significantly higher in the preeclampsia women than that of controls ($P < 0.001$). This is partly comparable to our study where the mean TSH and FT4 are significantly different between the groups with the PE group having a high mean TSH and a low mean FT4.

In another Indian study, the mean TSH titers in the preeclampsia pregnancies have been 3.8 ± 0.53 mIU/ml. In the normal pregnancies, it was 2.3 ± 0.24 mIU/ml (Kaliq fetal) which again is comparable to the present study.[16]

A study by Wilson *et al.*[17] women with subclinical hyperthyroidism had an incidence of hypertensive disorders of 6.2% compared with 8.5% of euthyroid women and 10.9% subclinical hypothyroid women. After adjusting only women with subclinical hypothyroidism were at increased risk for severe preeclampsia (adjusted odds ratio, 1.6; 95% confidence interval, 1.1–2.4; $P = 0.031$) pointing toward a causal role.

In the calcium for preeclampsia prevention cohort, the mean TSH values were increased 2.42 times above baseline in the PE group compared with a 1.48 times increase in controls (Levin *et al.*, 2009). Thus, this study suggests PE as a possible risk factor for hypothyroidism, and the mechanisms could be mediated through s-linked like tyrosine kinase.[18]

According to Ashoor *et al.*,[19] measurements of maternal serum TSH can improve late-PE prediction provided by a combination of factors in the maternal history and mean arterial pressure and uterine artery measurements pulsatility index.

Hypothyroidism may also play a direct role in causing pregnancy hypertension because thyroid hormones act directly on peripheral arterioles to cause dilation (Dernellis and Panaretou, 2002). On the other hand, there a few studies arguing against any relationship between hypothyroidism and preeclampsia. In the present study, the mean TSH is significantly higher in the preeclampsia group and FT4 being significantly lower.

The prevalence of subclinical hypothyroidism in our entire study group is 19.5% (28% in preeclampsia women and 11% in normotensive women) and overt hypothyroidism contributing to 2% preeclampsia group while 3% in normotensive group. The mean age of termination in the study group was 37–38 weeks (72%), while that in the control group was 39 weeks (79%) which allows 15% of postdated. This study also analyzed the relationship between the severity of preeclampsia and hypothyroidism. Out of the 100 preeclampsia patients, 26 belonged to the severe and 74 belonged to the mild preeclampsia group. The TSH was significantly more in the severe preeclampsia group as compared to mild preeclampsia (2.8 ± 1.67 vs. 2.4 ± 1.33); $P < 0.0001$).

The values of free T4 are (1.08 vs. 1.25) numerically less in severe preeclampsia than mild preeclampsia, and they were statistically significant ($P < 0.0001$). These findings strongly suggest an association between the severity of preeclampsia and hypothyroidism.

CONCLUSION

From this study, we concluded that the preeclamptics have a higher incidence of hypothyroidism (SCH) than the normotensive women. There is a correlation between the severity of preeclampsia and hypothyroidism. The treatment of OH and SCH is mandatory. In future, there should be a changing trend toward routine screening of hypothyroidism in contrast to targeted screening, but further, more extensive studies are needed to support this fact.

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Original Article

Study of Pulmonary Function with Rheumatoid Arthritis Disease Patients

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Abstract

Introduction: Rheumatoid arthritis (RA) is a multisystem disease of unknown cause. It is a common inflammatory arthritis and an important cause of potentially preventable disability. The characteristic feature of RA is persistent inflammatory synovitis usually involving peripheral joints both small and large in a symmetric distribution.

Aim: This study aims to study the association pulmonary function with the disease activity in RA.

Materials and Methods: This is a cross-sectional study was done in 25 patients with RA who have met the updated requirements of the American Rheumatological Association. All the data were gathered from the patients, and the patients received informed consent. The findings have been analyzed and, statistically, discussed below.

Results: Out of 25 patients, 9 patients were male, and 16 patients were female. The mean age of duration was 41.24 years, the mean duration of RA was 5.25 years, five patients had small airway obstructive diseases, four patients had restrictive pulmonary diseases, and three patients had large airway obstructive diseases. Nineteen patients were included in functional class 3 and 4, six patients were included in functional class 1 and 2. Cough presents in eight patients. Wheeze and crepitation present in two patients. Nineteen patients had a positive rheumatoid factor. Mean hemoglobin and ESR values are 11.41 and 62.42.

Conclusion: We concluded from this analysis that in RA patients, the prevalence of pulmonary function disorders was high. Males were more vulnerable to rheumatoid pulmonary diseases due to other habits. There was no link between RA duration and rheumatoid lung disease.

Keywords: Rheumatoid arthritis, Pulmonary function, Small airway disease

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that presents the most prominent manifestations in the diarthrodial joints.[1] The incidence of this disease is around 1% in the general population.[2] Symmetrical, disruptive, and deforming polyarthritis affecting small and large synovial joints with associated systemic disturbances is the most prevalent type of the disease. In addition to a number of extra-articular characteristics and the presence of antiglobulin circulating antibodies (rheumatoid factor).[3]

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Destructive polyarthritis and extra-articular organ involvement characterize the extra-articular types of RA.[4-6] Extra-articular characteristics and non-articular RA complications are standard and are typically associated with more severe morbidity and mortality. They need to be identified early and treated promptly.[7] Pulmonary involvements that can commonly be seen in patients with a high rheumatoid factor (RF) titer and smokers are one of the essential extra-articular manifestations of RA.[5]

RA patients have a high incidence of defects in their pulmonary system. In these patients, irregular lung functions can range from interstitial lung diseases (ILDs) to both large and small airway diseases. Both restrictive and obstructive patterns indicate lung abnormalities. Although not always clinically recognized, pulmonary involvement in RA is frequent. Pleural disease is widespread but generally asymptomatic; in 50% of cases, autopsy studies have reported pleural involvement, with only 10% clinical participation. Lung involvement is a significant contributor

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to the morbidity and mortality of RA patients and is the second most common cause of death, with infections being the first.

In RA patients, pulmonary involvement may be assessed as interstitial pneumonitis and fibrosis, pleural involvement, pulmonary nodule, pneumonia organizing bronchiolitis obliterans, pulmonary hypertension-related arthritis, and small and wide airway involvement.[8,9]

Another type of pulmonary manifestation in patients with RA who usually have a poor prognosis is interstitial ILD. RA-ILD mostly has no signs and is only diagnosed through clinical review, pulmonary function test (PFT), and high-resolution computed tomography (HRCT), so it seems that diagnosis of pulmonary involvement in early stages of RA is of great importance.[10-12]

Therefore in terms of history, clinical review, chest X-ray, PFT, and HRCT, we agreed to evaluate RA patients to verify that the assessment of RA patients without pulmonary symptoms is justifiable, rational, and cost effective using the methods described above.

Aim

This study aims to study the association pulmonary function with the disease activity in RA.

MATERIALS AND METHODS

This is a cross-sectional analysis was done in 25 patients with RA who meet the updated requirements of the American Rheumatological Association (ARA). Inclusion criteria: Patients who have completed the revised criteria of the ARA, regardless of whether there are respiratory signs or symptoms or not. Exclusion criteria: Bronchial asthma/chronic obstructive airway disorder, current/past lung tuberculosis, occupationally resistant patients, X-ray radiological lesion, and extreme pulmonary function test – interference-related disease patients with a detailed history of the disease period are evaluated. Exclusion criteria medical test assigned rheumatological functional status. A thorough examination of the respiratory system, with particular attention to chest growth, pleuritic, pleural effusion, and were done. The patients and controls submitted to computerized spirometric tests after reviewing these baseline clinical and laboratory parameters.

Data are presented as mean, percentage and number of instances, and standard deviations. The continuous data compared to independent t-tests, and the Pearson Chi-square tests compared categorical data.

RESULTS

Based on diseases parameters, mean value of the functional class is 1.58, the tender joint count is 5.62, hemoglobin is 11.41, and ESR is 62.42 [Table 1].

Out of 25 patients, 4 patients had restrictive pulmonary diseases, 3 patients had large airway obstructive diseases, and 5 patients had small airway obstructive diseases [Table 2].

Based on spirometric parameters, mean value of forced vital capacity (FVC) is 88.2, forced expiratory volume in 1 s (FEV1) is 84.51, FEV1/FVC is 94.82, forced expiratory flow (FEF) 50% is 78.91, and FEF 25–75% is 79.82 [Table 3].

Based on clinical features, 13 had age >40 years, 12 patients had age <40 years, 9 were males, and 16 were females, 8 patients had a duration of diseases >5 years, 17 had <5 years, 19 patients were included in functional class 3 and 4, 6 patients were included in functional class 1 and 2, 8 patients had the symptom of cough, and 17 patients had no cough, 19 patients had positive RF factor, and 6 patients had negative RF factor [Table 4].

Table 1: Rheumatoid arthritis activity parameters

Disease parameters	Mean (S.D)
Functional class	1.58
Tender joint count	5.62 (4.14)
Haemoglobin (g/dL)	11.41 (1.11)
Erythrocyte sedimentation rate (mm/h)	62.42 (28.61)

Table 2: Gender distributions of abnormal pulmonary function tests

PFT abnormality	Number of patients	Males	Females
	n=25	*n*=9	*n*=16
Restrictive	4	2	2
Large airway obstructive	3	1	2
Small airway obstructive	5	2	3
Total	12	5	7

Table 3: Pulmonary function tests

Spirometric parameter	RA patients	
	Mean	S.D
FVC	88.2	10.01
FEV 1	84.51	9.28
FEV1/FVC	94.82	11.25
FEF 50%	78.91	14.95
FEF 25–75%	79.82	16.42

Table 4: Clinical features of rheumatoid arthritis patients

Clinical feature	With abnormal PFT (*n*=9)	With normal PFT (*n*=16)
Age		
>40 years	3	10
<40 years	6	6
Gender		
Male	4	5
Female	5	11
Duration of disease		
>5 years	2	6
<5 years	7	10
Functional class		
III and IV	7	12
I and II	2	4
Cough		
Present	5	3
Absent	4	13
RF		
Positive	8	11
Negative	1	5

DISCUSSION

One of the most frequently linked extra-articular organs for RA is the lung. Pulmonary dysfunction in RA has a worse forecast. Provenzo *et al*.[13] observed in a sample of 24 RA patients that 2 patients have obstructive patterns and 1 patient has restrictive patterns. The majority of our study identified small obstructed lung disorders followed by restrictive conditions. About 20% had HRCT detected pleural disease. Perez *et al*.[14] observed broad 18% airway blockages in their sample of 50 RA patients; low 8% airway illnesses; and restrictive 8% lung disease. Malaviya *et al*.[15] observed pulmonary dysfunction in 8% in a North Indian RA sample.

The only risk factor in ILD development in RA was identified by Gabby *et al*.,[16] male gender. In this study, the patient's age and pulmonary impairment were not associated. The period of RA and lung activity was not associated. There was also a detrimental correlation with the magnitude of RA. Cortet *et al*.[17] and Gabby *et al*.[16] also showed similar results as a non-association. However, Vergnegeree *et al*.[18] have demonstrated that RA was associated with lung dysfunction severity. Perez *et al*.[14] have found FEV1/FVC to decrease, but not to a significant statistic. Geddes *et al*.[19] have encountered a considerable smoking and airway obstruction relationship. Collins *et al*.[20] have concluded that an increased PFT abnormality can be explained in RA alone by smoking. Saag *et al*.[21] stated that cigarettes are the most consistent independent risk factor for ILD growth. Davidson *et al*. also showed a strong association between smoking and reduced gas transfer during their study of PFT in RA patients. Cortet *et al*.[17] found that cough and bronchitis have been highly prevalent, and respiratory infections have played a lead in the pathogenesis of rheumatoid lung disease. A similar finding was observed. The study of 62 patients showed a significant correlation between RF positivity and reduced diffusion capacitance, which is also the basis of the substantial correlation between respiratory symptoms (cough and dyspnea) and airway diseases diagnosed by PFT and HRCT by Perez *et al*.[14] and Schernthaner *et al*.[22]

CONCLUSION

We concluded from this analysis that in RA patients, the prevalence of pulmonary function disorders was high. Males were more vulnerable to rheumatoid pulmonary diseases due to other habits. There was no link between RA duration and rheumatoid lung disease.

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Original Article

Evaluation of Post-operative Adhesive Intestinal Obstruction in a Tertiary Care Center

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Abstract

Introduction: Peritoneal adhesions are defined as abnormal fibrous bands between organs or tissues or both in the abdominal cavity that are normally separated. Post-operative adhesions are most common cause of intestinal obstruction. Clinical implications of post-operative bowel adhesions may be small bowel obstruction, secondary infertility, and chronic abdominal or pelvic pain, difficulty in peritoneal dialysis, difficulty in intraperitoneal chemotherapy, and difficulty in re-operation.

Materials and Methods: This is a prospective observational study conducted in 50 patients at SGT Medical College, Budhera, from June 2017 to June 2019. Patients admitted in emergency with diagnosis of post-operative intestinal obstruction were considered for study. Detailed history, examination and investigations were done. Patients without symptoms and signs suggestive of any ischemia/strangulation were put on conservative treatment. If the condition deteriorated, patients were considered for surgery. Statistical analysis was carried out as required.

Results: Male patients were more than female patients. Abdominal pain was most common presentation. Most of the patients presented within 4 days of start of symptoms. Patients with history of abdominal hysterectomy, intestinal perforations, and trauma had more chances of obstructions. Most of the patients presented within 5 years from surgery in past. Most of the patients had one episode of obstruction. Most patients got relief in 3–5 days. About 60% patients were managed conservatively. Bands due to adhesions were most common intraoperative findings.

Conclusion: Our study has enriched the literature that those patients who had undergone pelvic surgeries or laparotomy because of perforations, developed adhesions more commonly than others. If conservative treatment is done properly, some patients can be saved from surgery. We have also elaborated the factors which guide us about conservative or operative treatment.

Key words: Adhesion, Conservative, Intestine, Obstruction, Operative.

INTRODUCTION

Peritoneal adhesions are defined as abnormal fibrous bands between organs or tissues or both in the abdominal cavity that are normally separated. About 95% patients are expected to develop post-operative adhesions.[1] Fortunately most patients are symptomless, in others there may be significant morbidity and mortality. The adhesions start few hours after operation. Post-operative adhesions are most common cause (about 65%) of intestinal obstruction.[2] Adhesions occur due to peritoneal injury and inflammation. Fibrin is formed which may get reabsorbed due to inherent fibrinolytic activity of peritoneum, or get organized due to ingrowth of fibroblasts. Clinical implications of post-operative bowel adhesions may be small bowel obstruction,[3] secondary infertility, chronic abdominal or pelvic pain,[4] difficulty in peritoneal dialysis, difficulty in intraperitoneal chemotherapy, and difficulty in re-operation.[5] Due to adhesions laparoscopic approach is almost impossible.[6] Re-operative surgery for adhesions takes long time, blood loss is more and chances of inadvertent enterotomy are high.

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Patients with partial adhesive obstruction and without signs of peritonitis or strangulation can be put on conservative treatment. Conservative treatment involves nil by mouth, Ryle's tube aspiration, intravenous fluid, electrolyte imbalance

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correction, and clinical and radiological observations. Conservative treatment should be continued for 72 h. If close monitoring is done and signs suggestive of complications are not there, then conservative treatment can be continued for even more than 10 days. This is safer than surgery. However, if fever occurs at any time and total leucocyte count (TLC) is more than 15,000/mm^3, then conservative treatment should be stopped and surgery should be considered. Post-operative adhesive intestinal obstruction is a very common surgical problem. It should be resolved at the earliest. Protocols of conservative approach versus surgery have been given in detail, but still lacunae are there. We have proposed this study to enrich the literature, that due to which surgeries, maximum adhesions are formed. How meticulous conservative treatment can decrease the numbers of operations in post-operative intestinal obstruction and which are the factors which will guide us about stoppage of conservative treatment. This study will be a step in these directions.

MATERIALS AND METHODS

Study Design

This is a prospective observational study conducted at SGT Medical College, Budhera, Gurugram, Haryana, from June 2017 to June 2019.

Study Population

Patients admitted in emergency Department of General Surgery, SGT Medical College with diagnosis of post-operative intestinal obstruction were considered for study. Only those patients were included who had recurrent pain abdomen, distension, obstipation, and X-ray showing multiple air fluid levels or ultrasonographic (USG) or contrast-enhanced computed tomography (CECT) abdomen showing evidence of intestinal obstruction and the etiology was post-operative intestinal obstruction due to adhesions. The patients, who had laparotomy <50 days back, or the etiology of obstruction was other than adhesions were excluded from study. Those patients were excluded from study who had laparotomy within 50 days or who had causes of intestinal obstruction other than that due to adhesions.

Operational Definition

Here intestinal obstruction is due to peritoneal adhesions. Peritoneal adhesions are defined as abnormal fibrous bands between organs or tissues or both in the abdominal cavity that are normally separated.

Sample Size

Fifty patients were taken for study.

Sampling Procedure and Data Collection

Patients presenting with intestinal obstruction were considered. Among these, only those patients, who had etiology as adhesions, were considered for study. Even among these, if at a later stage, it was found that the obstruction was not due to adhesions, these patients were excluded from study. Detailed history including age, sex, address, occupation, duration of complaints, details of complaints, features suggestive of strangulation, history of features of intestinal obstruction, any history of admission in hospital, any history of operation in past, if yes, and type of operation was taken. General physical and systemic examination was done. Routine investigations, for example, complete blood count, kidney function tests, liver function tests, urine complete examinations, diabetic profile, and viral markers were done. Investigations to support the diagnosis, for example, plain X-ray abdomen and USG were done. CECT abdomen was done if there was diagnostic dilemma. These investigations were also repeated as per requirement. If patients had no pyrexia, tachycardia, tenderness, guarding, and rigidity and TLC was normal; if the symptoms and signs did not suggest any ischemia/strangulation; patients were put on conservative treatment for 3 days or even longer if vitals were stable. If patients got relieved of the symptoms, passed flatus, they were kept for 1 more day and on full relief, they were discharged, with advice regarding diet, and to report at earliest if symptoms recur. If the condition deteriorated, patients were considered for surgery, if done so, details of intraoperative findings, post-operative complications if any were recorded.

Analysis Plan

The data were collected properly on a performa sheet, data were tabulated and master chart was prepared, entries were made, and statistical analysis was carried out using simple mathematical expressions like, percentage. The data were subjected to appropriate statistical tests wherever applicable. Analysis was made using software SPSS for windows 7. Chi-square test and probability (*P*) value were used to establish status of significance. Quality of study was assured at each and every step.

Ethical Considerations

Before starting the study, approval for this study was obtained from the Institute Ethics Committee for research on human subjects. Written informed consent was obtained from each subject interviewed after asking them to go through the subject information sheet printed in Hindi language (in which subjects were well versed) and a verbal explanation by the interviewer. Confidentiality of the information provided was maintained.

RESULTS

This prospective observational study was carried in SGT Medical College, Budhera, Gurugram, Haryana. Fifty

patients, in whom etiology was intestinal obstruction due to adhesions, only were taken for study. Detail history was taken; physical examinations and investigations were done. Patients without any symptoms and signs of ischemia or strangulations were put on conservative treatment, if patients fared well, they were discharged. If patients had no relief with conservative treatment for 3 days, and patients developed signs and symptoms of ischemia or strangulation, they were considered for surgery. Following results were found.

In our study, age group 41–50 years had majority of 19 (38%) patients, and mean age of patients was 42.36 [Table 1]. Out of 50 patients 32 (64%) patients were male and 18 (36%) patients were female. Among males 14 (44.75%) patients, and among females 6 (33.33%) required surgery [Table 2].

Abdominal pain was present in all the patients, followed by vomiting, obstipation, and distention abdomen in decreasing frequency [Table 3]. Most of the patients presented within 4 days. They took this much time probably because they took treatment from some peripheral centers and became late [Table 4].

Our study reveals that most of the patients who had adhesive bowel obstruction had under gone exploratory laparotomy for abdominal hysterectomy, intestinal perforations, and trauma [Table 5].

In our study, most of the patients presented within 5 years from surgery in past. Some patients presented even 5 years after the past surgery [Table 6].

Our study shows that most of the patients 34 (68%) had one episode of obstruction. In 9 (18%), there were two episodes, in 4 (8%) three episodes and in 3 (6%), there were more than three episodes [Table 7]. We found that 12 (24%) patients had altered vitals, for example, tachycardia, fever, hypotension, etc. Seven (14%) patients had visible gut loops, 23 (46%) patients had exaggerated bowel sounds, and the bowel sounds were absent in 18 (36%) patients [Table 8].

Our most patients 20 (66.67%) got relief in 3–5 days. Some 3 (10%) patients took even 6–9 days [Table 9]. Most of the patients 30(60%) were managed conservatively; however, surgery was successfully done in 20 (40%) patients [Table 10].

We had operated 20 patients. In 6 (30%) patients, the adhesions caused constrictions, in 11 (55%) patients, bands had been formed due to adhesions and in 3 (15%) patients, there were matted adhesions [Table 11].

Table 1: Age distribution

Age	Number of patients (%)
15–0	2 (4)
21–30	9 (18)
31–40	10 (20)
41–50	19 (38)
>50	10 (20)

DISCUSSION

Abdominal adhesions cause great health problem utilizing lots of health care resources, deteriorating quality of life and loss of money. Diagnosis and management of adhesive intestinal obstruction has to be very careful. The conservative management is safe but the time of switching over to operative treatment is controversial. Our study is to enrich the literature regarding which are the surgeries, where maximum adhesions are formed. How meticulous conservative treatment can decrease the numbers of operations in post-operative intestinal obstruction and which are the factors which will guide us about stoppage of conservative treatment. This study is a step in these directions

This is a prospective observational study conducted at SGT Medical College, Budhera, Gurugram, Haryana, from June 2017 to June 2019, in 50 patients.

The mean age in our patients was 42.36 years [Table 1]. Our results are similar to study by Ngim *et al.* 2013,[7] Jain *et al.* 2015,[8] and Kang *et al.* 2010.[9] In our study, female population was less than male population [Table 2]. In studies by Hegre *et al.*,[10] also female population was less. It may be because female populations are more involved in household job; hence, trauma cases are less in them. Pain was presenting feature in all our patients followed by vomiting, obstipation, and distension abdomen [Table 3]. Pain was also seen in all patients in study by Hegde *et al.*[10] Vomiting was seen in 88% patients in study by Aldemir *et al.*[11] If Ryle's tube aspiration

Table 2: Sex distribution

Sex	Number of patients (%)	Conservative management (%)	Operative management (%)
Female	18 (36)	12 (66.67)	6 (33.33)
Male	32 (64)	18 (56.25)	14 (44.75)

Table 3: Intestinal obstructive symptoms

Symptoms	Number of patients (%)
Abdominal pain	50 (100)
Distention abdomen	31 (62)
Vomiting	48 (96)
Obstipation	42 (84)

Table 4: Duration of symptoms

Time period from onset of symptoms to reporting in hospital	Number of patients (%)
Within 4 days	42 (84)
>4 days	8(16)

Table 5: History of operation in past

Past operation	Emergency	Elective	Percentage
Peptic perforation	8	-	16
Enteric perforation	9	-	18
Cholecystectomy	-	3	6
Abdominal hysterectomy	-	10	20
Appendectomy	5	-	10
Abdominal wall hernia	-	3	6
Trauma	12	-	24

Table 6: Duration between surgery in past and adhesive bowel obstruction.

Duration between surgery in past and adhesive bowel obstruction	Number of patients (%)
<2 years	18 (36)
2–5 years	23 (46)
>5 years	9 (18)

Table 7: Episodes of adhesive bowel obstruction

Episodes of adhesive bowel obstruction	Number of patients (%)
1 episode	34 (68)
2 episodes	9 (18)
3 episodes	4 (8)
>3 episodes	3 (6)

Table 8: Clinical findings at admission

Clinical findings	Number of patients (%)
Altered vitals	12 (24)
Visible gut loops	7 (14)
Bowel sounds exaggerated	23 (46)
Bowel sounds absent	18 (36)

Table 9: Duration of relief of symptoms

Duration of relief of symptoms (days)	Number of patients (%)
1	3 (10)
2	4 (13.33)
3	8 (26.67)
4	7 (23.33)
5	5 (16.67)
6–9	3 (10)

Table 10: Management

Management	Number of patients (%)
Operative	20 (40)
Conservative	30 (60)

Table 11: Operative findings

Operative findings	Number of patients (%)
Constrictions	6 (30)
Bands	11 (55)
Matted adhesions	3 (15)

is large in volume, it suggests persistent intestinal obstruction. Feculent vomiting suggests requirement of surgical intervention. Most of our patients presented late [Table 4], probably because in our set up patient first goes to very small centers with limited resources and when there is no relief, then he attends tertiary care centers. Regarding history of operations in past, we have found that more cases are from pelvic surgery, appendectomies, and perforations [Table 5]. It is possibly so, because small bowel shifts to site of surgery in lower abdomen or pelvis forming stronger adhesions. Increased incidence of adhesions in perforations may be due to infections. In our study, maximum cases had obstructions within 5 years [Table 6]. The results of studies by Menzies 1990[1] and by Jain *et al.* 2015[8] are similar to our studies. We have found that maximum patients had only one episode of obstruction, but some patients had two, three, or more than three episodes [Table 7]. The reason may be that patients, who had one episode, might have more in future, because still whole life is before them. We have seen that most patients had bowel sounds exaggerated [Table 8] because probably these were the patients who had presented early. Our 30 (60%) patients got relieved by conservative treatment. Out of these, most got relief in 3–4 days. Some took even 6–9 days [Table 9]. This study teaches us that we should treat patients conservatively meticulously and if vitals are stable, the conservative treatment may be carried on for longer time because conservative treatment is better than surgery. With meticulous care, operation had to be performed only in 20 (40%) patients [Table 10]. Intraoperative findings of our study revealed that bands due to adhesions were the cause of obstruction in maximum patients followed by constrictions and matted adhesion. These results are almost comparable with the results of study by Jain *et al.*[8]

CONCLUSION

Our study has enriched the literature that those patients who had undergone pelvic surgeries or laparotomy because of perforations, developed adhesions more commonly than others. If we do conservative treatment in a meticulous way, keeping an eye on vitals and radiological findings, we can save some more patients from surgery. We have also elaborated the factors, that is, fever, tachycardia, tenderness, rigidity, guarding and raised TLC, which if present, guide us about the stoppage of conservative treatment and switching over to operative treatment.

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Original Article

A Study on Prevalence of Gestational Diabetes in Urban Field Practice Area of Tertiary Health-Care Center of Hyderabad

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Abstract

Introduction: Abnormal sugar levels which were detected 1st time during pregnancy are called gestational diabetes mellitus (GDM). According to the WHO, diabetes mellitus during pregnancy should be diagnosed if one or more of the following criteria are met: Fasting plasma glucose 7.0 mmol/L (126 mg/dL), 2-h plasma glucose 11.1 mmol/L (200 mg/dL) following a 75 g oral glucose load, and random plasma glucose 11.1 mmol/L (200 mg/dL) in the presence of diabetes symptoms. GDM had become global burden and leading cause of morbidity and mortality among mothers and infants contributing to infant mortality rate (IMR) and maternal mortality rate (MMR) worldwide.

Materials and Methods: A community-based cross-sectional study was conducted among pregnant women and sample size of 500 was attained by visiting the Anganwadi centers in urban slums under filed practice area of Osmania medical college, pregnant women of ≥20 weeks of gestational age were included in the study and data were collected using questionnaire, and GDM was diagnosed based on 2013 WHO publication of diagnostic criteria and classification of hyperglycemia first detected in pregnancy.

Results: A total of 500 pregnant women were included in this study, mean age of study population = 24.26 ± 3 years, mean age of marriage = 21.5 ± 2.747 years, mean gestational age in weeks = 28.38 ± 4.522, average weight gain among total population = 6.04 ± 1.848, and prevalence of the GDM was 19% (*n* = 95).

Conclusion: The present study documented prevalence of 19% of GDM which has to be addressed to overcome the complication associated with it and also to decelerate the trends of IMR and MMR.

Key words: >20 weeks, Gestational diabetes mellitus, Urban slums

INTRODUCTION

Abnormal sugar levels which were detected 1st time during pregnancy are called gestational diabetes mellitus (GDM). According to the WHO, diabetes mellitus during pregnancy should be diagnosed if one or more of the following criteria are met: fasting plasma glucose 7.0 mmol/L (126 mg/dL), 2-h plasma glucose 11.1 mmol/L (200 mg/dL) following a 75 g oral glucose load, and random plasma glucose 11.1 mmol/L (200 mg/dL) in the presence of diabetes symptoms.[1] GDM had become global burden and leading cause of morbidity and mortality among mothers and infants contributing to infant mortality rate (IMR) and maternal mortality rate (MMR) worldwide.[2-7]

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Impact of Diabetes Mellitus on Mother and Neonate

GDM not only triggers the immediate outcomes among pregnant mothers such as preeclampsia, macrosomia, stillbirths and atonic uterus and neonatal outcome, hypoglycemia, and respiratory distress. GDM further increases the risk of development of type-II diabetes mellitus not only among mothers after deliver but also

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among babies. A meta-analysis study done by Bellamy *et al.* concluded that there is a higher risk of type-II diabetes among women with GDM with a relative risk 7.43, 95% confidence interval 4.79–11.51.[8,9]

Global Scenario and Indian Scenario

According to international diabetes federation 2019 report, there are about 20 million of live births had some form of hyperglycemia during pregnancy, of with 84% of hyperglycemia was due GDM, one out of six births are affected by GDM globally, low- and middle-income countries have wider had higher episodes of hyperglycemia during pregnancy.[10]

The prevalence of gestational diabetes in India had varied from state to state ranging from 3.8% in Kashmir,[11] 9.5% in Western India,[12] 17.9% in Tamil Nadu,[13] in Punjab, it was 35%,[14] in Lucknow, it was 41%.[15]

Risk Factors of GDM

GDM is mostly associated with maternal obesity, lack of physical activity, family history of gestational diabetes, previous history of GDM, previously delivered baby weight more than or equal to 4 kgs, polycystic ovarian syndrome, etc., which are some of the risk factors for GDM.

Aim

This study was the prevalence of gestational diabetes in urban field practice area of tertiary health-care center of Hyderabad.

Objectives

The objectives of this study were as follows:

1. To estimate the prevalence of GDM.
2. To study the sociodemographic factors of study population and associated risk factor of GDM.

MATERIALS AND METHODS

Study area: Urban field practice area of Osmania medical college.

Study design: Cross-sectional study.

Study units: Pregnant mothers.

Sampling technique: Convenient sampling technique was followed.

Sample size: Using 4 pq/L2, considering the prevalence of $P = 17.8\%$ from Seshiah *et al.* study,[16] with allowable relative error of 20% and L = 3.56, sample size of $n = 443.5$ is attained and considering the non-responsive rate of 10%, sample size of 487.5 is attained which is rounded up to $n = 500$.

Study period: Three months (October to December 2017).

Inclusion Criteria

Pregnant women of ≥20 weeks of gestational age and who gave consent to participate in the study were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. Pregnant women who did not gave consent to participate in the study.
2. Pregnant women <20 weeks of gestation, and established diabetes mellitus (Type II), pregnant women with chronic illness.
3. Pregnant women with other medical complications.

Data Collection

Data were collected from all the pregnant women of gestational age ≥20 weeks of gestational age who were visiting primary health-care center (PHC) of Harazpenta, Hyderabad, for regular antenatal check-ups, questionnaire was used for collecting data, random blood sugars (RBS) testing was done to all pregnant women of ≥20 weeks of gestation, pregnant women with RBS of >146 mg/dl were advised for fasting blood sugars (FBS), and data were collected accordingly, data were analyzed using Microsoft Excel 2010 version and open Epi version 3.3.0.

Need for the Study

Gestational diabetes is most important risk factor which contributes to IMR and MMR. Addressing this condition during pregnancy can reduce the morbidity and mortality pattern among pregnant women and newborns, due to varied knowledge gap into the existing topic, and as very limited number of studies were done on GDM.

RESULTS

The present study was conducted among $n = 500$ pregnant women who were residing in the urban slums, of which $n = 95$ (19%) were diagnosed with GDM. The prevalence of GDM among pregnant women was $P = 19\%$.

- Among study population 63% were Hindus, 29.2% Muslims, and 7.8% others.
- Mean age of study population = 24.26 ± 3 years.
- Mean age of marriage = 21.5 ± 2.747 years.
- Mean gestational age in weeks = 28.38 ± 4.522.
- Mean body mass index (BMI) = 23.19 ± 3.24.
- Average weight gain among total population = 6.04 ± 1.848.

The prevalence of GDM was more among study population belonging to middle class according to socioeconomic class with a prevalence of 11.8% followed by upper middle class

accounting for 5% and lower middle class accounted for 2.2% [Tables 1 and 2] [Figure 1].

Table 1: The distribution of study population based on sociodemographic variable and percentage of GDM among study population

Variable	Total *n*=500 (%)	GDM *n*=95 (%)
Age (years)		
16–20	66 (13.2)	8 (8.4)
21–25	252 (50.4)	18 (18.95)
26–30	165 (33)	58 (61.05)
>31	17 (3.4)	11 (11.57)
Socioeconomic class-based on BG Prasad classification		
Upper class	9 (1.8)	-
Upper middle class	125 (25)	25 (26.31)
Middle class	308 (61.6)	59 (62.10)
Lower middle class	54 (10.8)	11 (11.578)
Lower class	4 (0.8)	-
Distribution based on body mass index (based pre-pregnancy weight in kg)		
<18.55	20 (4)	4 (4.21)
18.55–24.9	298 (59.6)	22 (23.157)
25–29.9	165 (33)	58 (61.05)
>30	17 (3.4)	11 (11.578)
Parity		
Primiparity	360 (72)	59 (62.105)
Multiparity	140 (28)	36 (37.895)
Type of marriage		
Consanguineous	69 (13.8)	14(14.736)
Non-consanguineous	431 (86.2)	81 (85.26)

GDM: Gestational diabetes mellitus

DISCUSSION

The present study was conducted among pregnant women with a gestational age of ≥20 weeks of gestation a total of n = 500 pregnant women were included in the study, the prevalence of GDM was P = 19% in our study which was as similar to Seshiah *et al.*,[16] that is, P = 17.8%. The prevalence of GDM was found to be more prevalent in urban slums and urban area compared to rural areas as concluded by Seshiah *et al.*[16]

Our study showed that GDM was more prevalent among pregnant women who were <24 years of age group compared to that of women of >24 years of age which showed the associated based on age and GDM with

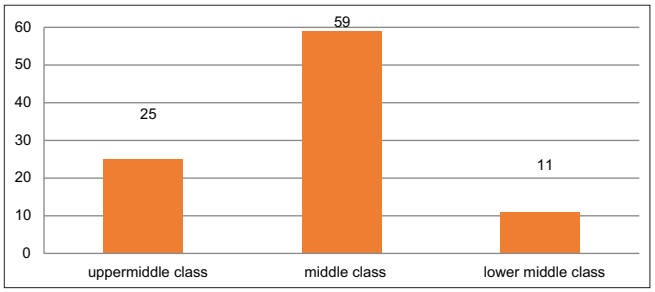

Figure 1: The distribution of study population based on socioeconomic class

Table 2: Association between risk factors and GDM

Variable	GDM+	GDM–	Total (*n*=500)	Chi-square *P*-value
Age in years				χ^2=43.16
≤24	21	241	262	*P*=0.0000
>24	74	164	238	df=1
Parity				χ^2=5.96
Primiparous	59	301	360	*P*=0.017
Multiparous	36	104	140	df=1
Association between BMI				
<18.55	4	16	20	χ^2=77.1
18.55–24.99	22	276	298	*P*=0.000001
25–29.99	58	107	165	df=3
≥30	11	6	17	
Association between family history of GDM				
Present	49	11	60	χ^2=169.7
Absent	46	394	440	*P*=0.0000001
				df=1
History of consanguinity				
Consanguineous	14	55	69	χ^2=0.08
Non-consanguineous	81	350	431	*P*=0.78
				df=1
Association between infertility treatment and GDM				
Present	29	96	125	χ^2=1.06
Absent	66	309	375	*P*=0.78
				df=1

*There was a significant association between age, parity, family history of GDM, and BMI and there was no significant association between history of consanguinity and infertility treatment with gestational diabetes mellitus
GDM: Gestational diabetes mellitus, BMI: Body mass index

$P = 0.000$, there was also an association between parity and GDM, primiparous women are more susceptible to GDM compared to multiparous women with a $P = 0.017$, family history of GDM was also a risk factor for GDM with a significant $P = 0000001$ which was similar to Geeti *et al.*[14] who conducted study among 5100 pregnant women.

Limitation

1. The present study followed convenient sampling technique at the PHC level.
2. RBS and FBS were only considered for concluding the prevalence of GDM.

CONCLUSION

The present study documented the prevalence of 19% of GDM which has to be addressed to overcome the complication associated with GDM and also to decelerate the trends of IMR and MMR.

There was a statistically significant association that was found between age group ($P < 0.00$), parity (0.017), BMI ($P < 0.00$), and family history of GDM ($P < 0.00$). Statistical insignificance is seen among consanguineous and non-consanguineous ($P < 0.768$) type of marriage and among women who underwent infertility treatment and those who did not undergo treatment ($P < 0.167$).

Pre-conceptional counseling should be given to all women about risk factors of GDM in mother and outcome in the baby, universal screening of pregnant women should be done with FBS level. Educating adolescent girls and reproductive age group women the role of regular physical activity , dietary modifications and healthy lifestyle in preventing GDM.

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Original Article

Aural Foreign Bodies and Their Management – A Retrospective Study

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Abstract

Introduction: Accidental insertion of foreign bodies in the external auditory canal continues to be a common problem in children and also nowadays common in adults due to overusage of earbuds. It is a relative medical emergency.

Aim: This study aims to study the clinical presentation of foreign bodies and their complications and management.

Materials and Methods: This is a retrospective study of 225 patients both adults and children who attended ENT Department at Institute of Child Health and Hospital for Children (ICH) and Rajiv Gandhi Government General Hospital (RGGGH) attached to Madras Medical College, Chennai.

Results: A total of 225 patients with aural foreign bodies were evaluated. In our series, the most common age group was between 0 and 4 years, particularly males were affected. Majority of them gave the history of foreign body insertion. The most common foreign body was seeds in the children and cotton buds in the adults. Majority cases managed without anesthesia.

Conclusion: Aural foreign bodies are very common presentation, particularly in children. The study aimed to diagnose the underlying cause for the foreign body insertion and to prevent dreaded middle ear complications using proper technique with appropriate instruments and if needed general anesthesia.

Key words: Ear, Foreign body, Management

INTRODUCTION

Aural foreign bodies are very common presentation at the ENT outpatient department. They are most common in the pediatric age group. Children put objects in their ears because they are curious or copying other children or during play, a whim to explore orifices, preexisting disease in ear causing irritation, and habitual cleaning of ear with objects like earbuds.[1,2] In adults, itching is one of the main reasons for the usage of different objects such as cotton buds match stick, pins to clean, or scratch the ear canal.[3]

Aural foreign bodies can be either inert or irritant, organic or non-organic, or hydrophobic or hydrophilic.[4] The most common inanimate foreign bodies are cotton bud, pins, beads, seeds, small stones, match stick, piece of paper, and small plastic objects. Among the animate foreign bodies, insects such as ants, bugs flies, and cockroaches are common. Insects will create a sense of constant irritation and some insects will damage the tympanic membrane. In discharging ears, flies are attracted to the foul smell and lay eggs which hatch out into larvae called maggots.[5]

In infants and younger children, aural foreign bodies will be an incidental finding. Some present with pain and discharge. Older children will give a clear history of insertion of a foreign body into the ear and give information about the foreign body type. Adults often present with a cotton bud or broken matchsticks used to clean the ear canal. They will have ear pain and mild serous ear discharge.

The ear and external auditory canal are richly supplied by the vagus nerve (Arnold's nerve), the auriculotemporal branch of the mandibular nerve, and a small facial nerve branch. This is why some patients will have severe ear pain and facial palsy occasionally.[6]

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Aural foreign bodies can be removed commonly and safely by irrigation with lukewarm water or aural forceps, and suctioning. Aural foreign bodies can be removed under direct visualization with proper light and with the good cooperation of the patient. In the pediatric age group, child cooperation is very important, or the attendee should hold the child properly throughout the procedure; otherwise, the foreign body can be removed under general anesthesia. Majority of aural foreign bodies can be removed by aural syringing. Cotton wool, large live insects, can be removed using aural forceps. Button batteries should be removed immediately as an emergency procedure.[7] Aural foreign bodies if not handled properly, it may lead to edema and lacerations in the external auditory canal, tympanic membrane perforation, injury to middle ear structure causing hearing loss, membranous labyrinth damage, and even facial palsy.

Aim

This study aims to study the clinical presentations and management of aural foreign bodies.

MATERIALS AND METHODS

This retrospective study was done in both pediatric department (ICH&HC) and RGGGH both attached to Madras Medical College, Chennai. This study includes 128 pediatric and 97 adults, between January 2018 and December 2020. All patients reported with a history of aural foreign body insertion were included in the study. Those patients with no suggestive history, but were found to have the foreign body are also included in the study. Detailed data of each patient concerning the age, sex, type of foreign body, and presenting symptoms were collected. A thorough examination of the ear was done, and any injuries and scar marks were noted. Any discharge was carefully suctioned out to ascertain the nature and a better view of the foreign body. The other ear, nose, and throat were also examined for any foreign body. Majority aural foreign bodies were removed by aural syringing. Cotton wool, big live insects, was removed by aural forceps. Majority of foreign bodies removed without anesthesia. Very few pediatric cases required local or general anesthesia.

RESULTS

In our study, a total of 225 cases presenting with aural foreign bodies were studied. Number of males was 123 while females were 102, less than 12 years are most common age group [Table 1].

In our study, the most common aural foreign body was seeds of various vegetables and fruits seen in 70 cases out of the total 225 cases. The next common was cotton buds seen in 37 cases not only in children but also adults. Insects were seen in 23 cases. Stones were seen in 12 cases [Table 2 and Figure 1].

In our study, majority of the patients 115 out of 225 presented with the history of foreign body insertion in the ear, either by the patients or by parents in case of infants and young children. The next presenting symptom was foreign body sensation which was seen in 22 cases. Other symptoms were ear pain, ear discharge, ear block, and bleeding [Table 3].

Table 1: Age and sex distribution of cases

Years	Male	Female	Number of cases	Percentage
0–5	35	30	65	28.9
6–12	33	30	63	28
13–20	30	24	54	24
21–40	13	10	23	10.2
>40	12	8	20	8.9
Total	123	102	225	100

Table 2: Distribution of foreign bodies

Foreign body	Number of cases	Percentage
Seeds	70	31.1
Cotton buds	37	16.4
Insects	23	10.2
Stones	12	5.3
Eraser pieces	9	8.4
Plastic objects	11	4.9
Match stick	10	4.4
Paper	9	4
Grains	7	3.1
Metal screws	7	3.1
Ear rings	5	2.2
Button battery	5	2.2
Stickers	5	2.2
Pins	4	1.8
Glass pieces	3	1.3
Metal ball	4	1.8
Pencil lead	4	1.8
Total	225	100

Figure 1: Foreign bodies

In our study, majority of cases 130 out of 225 aural foreign bodies were removed without any anesthesia. For infants and young children, around 50 cases foreign body removal done by general anesthesia. Adult in cooperative patients under local anesthesia aural foreign bodies removed in 35 cases [Table 4].

Complications which happened were observed due to the presence of foreign body and/or during and after removal.

Most of the cases did not develop complications 86.2%. The main complications were canal abrasions 4.5%, canal lacerations/bleeding 4.5%, otitis externa 3.1%, tympanic membrane perforation 2.2%, otitis media 0.9%, and facial palsy 0.4% [Table 5].

DISCUSSION

Aural foreign bodies are a common presentation in the ENT department, particularly the pediatric ENT outpatient department. Aural foreign bodies are common in the pediatric age group, as children are curious to explore their ears and thereby lodge objects inside the ear. In our study, the most common age group was under 12 years, constituting 56.9% of cases, 0–5 years constituted 28.9% of the total 225 cases. This observation is similar to the study done by Mazumder *et al.* who had 60% of cases under 14 years.[8]

Table 3: Distribution of symptoms

Symptoms	Number of cases	Percentage
History of foreign body insertion present	115	51.1
Foreign body sensation	22	9.8
Pain	20	8.9
Ear discharge	18	8
Ear block	16	7.1
Ear bleeding	12	5.3
Hearing impairment	12	5.3
Incidental finding	10	4.5
Total	225	100

Table 4: Type of anesthesia used for foreign body removal

Type of anesthesia	Total number of cases	Percentage
No anesthesia	130	57.8
General anesthesia	60	26.7
Local anesthesia	35	15.5
Total	225	100

Table 5: Complications of aural foreign bodies

Complications	Number of cases	Percentage
No complications	194	86.2
Canal abrasion	10	4.5
Canal laceration/bleeding	6	2.7
Otitis externa	7	3.1
Tympanic membrane perforation	5	2.2
Otitis media	2	0.9
Facial palsy	1	0.4

In our study, we observed more male patients 123 compared to female 102 out of the total 225 cases with male-to-female ratio 1.2:1. This observation is similar to the study of Tonga *et al.* who had 1.4:1 ratio.[9]

In our study, the most common aural foreign body was seeds of fruits and vegetables in 70 out of 225 cases, 31.1%. Next common foreign body was cotton bud in 37 cases. Insects seen in 23 cases. Our study correlates with the study of Chai *et al.*, in which seeds or nuts were the most common ear foreign body found in 47.1%.[10]

The majority of the aural foreign bodies 130 out of 225, 57.8% of cases were removed without anesthesia in the ENT outpatient department itself. For infants and young children 60 out of 225, 26.5% of cases general anesthesia was employed. Study conducted by Mazumder *et al.* on 148 cases of aural foreign bodies, 92.89% of cases of foreign bodies removed without anesthesia, and 8.11% of cases removed with general anesthesia.[8]

The above study does not correlate with our study. In our children hospital, majority of infants and young uncooperative children, aural foreign bodies removed under general anesthesia as an emergency procedure in our pediatric operation theater functioning round the clock. All our foreign bodies were removed by permeatal approach except in one pediatric case with the stone that has lodged through a perforation in the tympanic membrane. We removed by post-aural approach under general anesthesia.

Complication due to the presence of foreign body or extraction was uncommon; no complication was recorded in 86.7% of cases in our study in contrast to Sing *et al.* study, which recorded 77%.[11] Adequate immobilization and proper instrumentation allow the uncomplicated removal of many aural foreign bodies in the pediatric age group. The use of general anesthesia is preferred in infants and young children with an aural foreign body whose contour, composition, or location predispose to traumatic removal in the ambulatory setting.

CONCLUSION

Aural foreign bodies are very common presentations, particularly in the pediatric age group. Although not an emergency, the child with the aural foreign body is often anxious for the parents and should be diligently managed. Majority of the aural foreign bodies can be removed easily and safely with syringing lukewarm water, provided that the patient

should not have otitis media with perforation. With the proper illumination, appropriate instrument, and patient cooperation, we can avoid dreaded complications. In the case of infants and cooperative patients, general anesthesia is preferred. The endoscope and microscope role is relevant in medially placed foreign bodies and in case of tympanic membrane perforation. Permeatal approach used to remove the majority of foreign bodies, but post-aural approach should be considered for deep foreign bodies which have lodged through a perforation in the tympanic membrane into the unreachable middle ear space. Adults presenting with aural foreign bodies are less common, and underlying cause like skin allergies in the external canal and psychiatric condition should always be diagnosed. In pediatric age, unresolved persistent ear discharge after giving local antibiotics should look for any forgotten foreign body.

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Original Article

Voice Disorders and Reflux Disease – A Prospective Study

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Abstract

Introduction: Reflux laryngitis is a voice disorder that results from irritation and swelling of the vocal cords due to the backflow of stomach fluids into the throat. This backflow is called laryngopharyngeal reflux disease (LPRD) (acid that reaches the level of the throat). LPRD is one of the overlooked causes in patients with voice disturbance.

Aim: This study aims to study voice disturbances in 50 patients with suspected LPRD.

Materials and Methods: In this prospective study, 50 patients with suspected LPRD were included. The diagnosis was made based on the patient's history, video laryngoscopy, esophagoscopy, and the lower esophageal mucosa's biopsy. All the LPRD patients were treated with tab. rabeprazole 20 mg for 8 weeks. All the patients subjectively evaluated their voice problems using the Voice Handicap Index (VHI) questionnaire after treatment.

Results: The results of VHI showed the severity of the voice problems of the patients with LPRD. Video laryngoscopy and history proved LPRD in all 50 patients. Esophagoscopy, combined with the esophageal biopsy, detected signs of possible GERD in 40 patients (80%). Video laryngoscopy, combined with a subjective voice assessment, performed based on VHI before and after treatment with a proton-pump inhibitor showed a significant improvement.

Conclusion: Video laryngoscopy assessment of the laryngeal mucosa and esophagoscopy supplemented with a biopsy of the lower esophageal mucosa, showed to be a convenient diagnostic method when GERD and LPRD were suspected. Rabeprazole, a proton-pump inhibitor, proved to be very useful in the treatment of LPRD.

Key words: Laryngopharyngeal reflux, Proton-pump inhibitor, Voice disorders

INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as the reflux of stomach contents into the esophagus with pathohistological changes of the mucous membrane. When this reflux affects the laryngeal and pharyngeal mucosa, it is termed laryngopharyngeal reflux disease (LPRD).[1,2] Esophageal mucosa has a protective mechanism against aggressive factors of stomach contents, and it remains intact when physiological reflux happens in the night. The laryngeal lining above the upper esophageal sphincter is not as strong a protective lining and so when acidic contents of stomach reflux into the larynx they get irritated and inflamed.[3] Laryngeal and pharyngeal mucosa are very sensitive, and the acid peptic reaction of the stomach contents rapidly leads to mucosal injury. LPRD commonly occurs in daytime due to upper esophageal sphincter dysfunction.[4] The most common part of larynx affected is the posterior half including the arytenoids, interarytenoid junction, and post 1/3 of vocal cords. The esophageal reflux manifests as heartburn, belching, frequent clearing of throat, regurgitation, and bitter taste. The most typical extraesophageal manifestation includes hoarseness of voice. Others include persistent cough, choking episodes, and breathing difficulty.[5] In day-to-day practice, LPRD is mostly not recognized as it is a silent reflux and diagnostic and therapeutic protocols are insufficient. Due to the high prevalence of disease and varied clinical manifestations, most patients report to family physicians. Improper clinical evaluation and inadequate diagnostic options are the biggest challenges in treating reflux effectively. Proper understanding of the etiopathogenesis plays a significant

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role in treating GERD and LPRD. Untreated LPRD can lead to laryngeal cancer.[6] The development of the disease can be life threatening considerably affecting the quality of life. In our study, we have focused on the importance of diagnostic options, including proper clinical history, clinical evaluation, video laryngoscopy, esophagoscopy, and biopsy of the lower esophagus. The patients are treated with proton-pump inhibitors for 8 weeks along with weight reduction, lifestyle modification, and dietary alterations. The improvement of voice after treatment is assessed with Voice Handicap Index (VHI) questionnaire.

Aim

This study aims to study voice disturbances in patients with suspected laryngopharyngeal reflux disease.

MATERIALS AND METHODS

In this prospective study, 50 patients between the age group of 18 and 45 years who presented to the Outpatient Department of ENT in Sree Balaji Medical College and Hospital, with laryngopharyngeal problems in whom GERD was suspected were included in the study. The diagnosis of LPRD was made based on the patient's history and video laryngoscopy using a 45° rigid endoscope. All the LPRD patients were treated with rabeprazole (20 mg) once a day for 8 weeks, combined with appropriate dietary and lifestyle changes. All the patients subjectively evaluated their voice problems using the VHI questionnaire before and after the treatment. Before the treatment, the esophagoscopy and the mucosa biopsy in the lower third of the esophagus were performed for all 50 LPR patients.

Typical esophagitis above the lower esophageal sphincter, hiatal hernia, or dysfunctional lower esophageal sphincter indicated GERDs possibility. Intraepithelial eosinophils, basal zone thickening, and papillary lengthening in the esophageal biopsy specimen were supposed to indicate the prolonged acid reflux. The biopsy was marked as positive when all three criteria were fulfilled. The histologic examination of the esophageal specimens was compared to the results of the esophagoscopy and video endolaryngoscopy. The results of the video endolaryngoscopy and VHI questionnaire were compared, before and after the treatment with rabeprazole.

RESULTS

The main symptoms of the LPRD patients were hoarseness (30 patients), throat clearing (10 patients), and globus pharyngeus sensation (10 patients), two of them being simultaneously present in all LPRD patients [Figure 1].

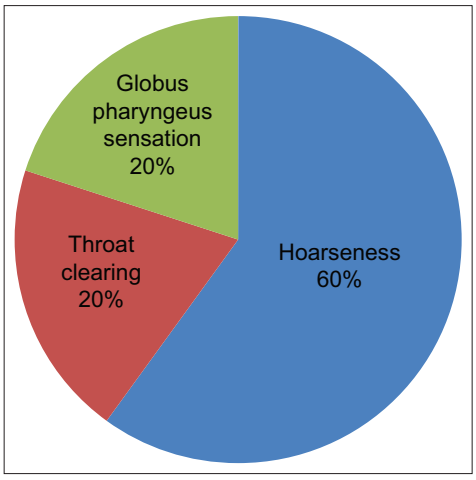

Figure 1: Distribution of symptoms

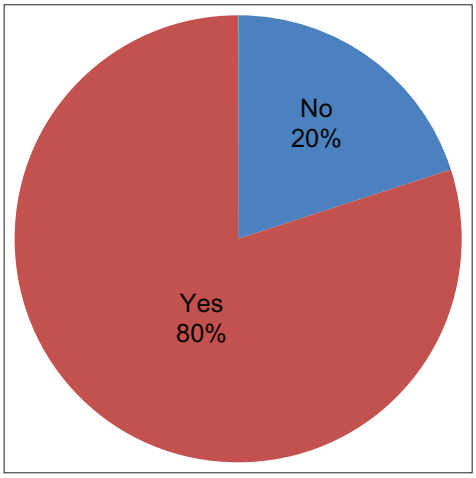

Figure 2: Distribution of GERD in study patients

After the treatment with rabeprazole, the LPRD patients felt relief and felt that their problems decreased by 20% as per the VHI. Esophagoscopy confirmed the possibility of GERD in 14 LPRD patients. The histopathological examination of the esophageal biopsy specimens indicated prolonged acid reflux in 20 patients in whom esophagoscopy did not detect any signs of reflux esophagitis, hiatal hernia, or dysfunctional lower esophageal sphincter. Both examinations, when combined, detected signs of possible GERD in 40 patients (80%) [Figure 2]. Video endolaryngoscopy and history proved extraesophageal or LPRD in all 50 patients.

DISCUSSION

Our study confirmed that LPRD could cause considerable voice problems. The appropriate treatment with a proton-pump inhibitor significantly reduces a patient's problems. In GERD and LPRDs diagnostics, the patient's history and video laryngoscopy are superior to the esophagoscopy.

Esophagoscopy with a biopsy of the esophageal mucosa is a convenient diagnostic method when GERD and LPRD are suspected. The diagnosis of LPRD is based on a patient's symptoms, laryngeal findings, and subjective results. Some GERD is physiologic, occurring mostly after meals.

Ambulatory 24 h double probe (simultaneous esophageal and pharyngeal probes) with pH monitoring is the most suitable diagnostic method. On the other hand, several studies proved that evident signs of LPRD could be detected, even in patients with negative 24 h pH monitoring.[7] It was also proved that pepsin is activated, even in values of pH higher than 4.[8]

LPRD is known to contribute to posterior acid laryngitis, laryngeal contact ulcers or granuloma formation, epithelial dysplasia and laryngeal cancer, chronic hoarseness, pharyngitis, sore throat, globus sensation, dysphagia, buccal burning, asthma, pneumonia, nocturnal choking, and dental diseases. These manifestations are believed to be caused by direct contact of the gastric content and injury to the pharyngeal or laryngeal mucosal surfaces. Acid reflux inside the distal esophagus itself also stimulates vagally mediated reflexes, leading to bronchospasm and coughing disorders.[9]

Extraesophageal reflux can cause damage to the laryngeal mucosa from coughing, voice abuse, intubation, or lower respiratory tract infection. LPRD has been implicated as being causative or contributory in laryngeal pathologic states such as vocal nodules, Reinke's edema, and scar formation as in idiopathic subglottic stenosis, functional laryngeal movement disorders such as muscular tension dysphonia, paradoxical vocal fold motion, and paroxysmal laryngospasm. LPRD also lowers the cough threshold.[10]

In GERD patients, the occurrence of extraesophageal symptoms is as high as 67%.[11] There are many patients with voice disorders who have LPRD as the main or one of the important reasons for their dysphonia. An endoscopic examination of the larynx usually reveals the signs of LPRD with arytenoids congestion, axed vocal cords gap, but the scenario requires a combination of more diagnostic procedures to confirm the clinical suspicion of GERD and LPRD.

In our study, the results of the video laryngoscopy correlated very well with the histological findings of the esophageal mucosa specimens. Video laryngoscopy is a very simple method, which can be easily repeated and is well tolerated by the patients.

LPRD patients can be treated with dietary and lifestyle modifications, alginates, and proton-pump inhibitors. The results of our study confirmed that the treatment with rabeprazole was successful. Our patients assessed that their problems (dysphonia, globus pharyngeus sensation, throat clearing, etc.) decreased after the 2-month therapy. Further improvement is expected with prolonged rabeprazole treatment.

The subjective assessment of voice problems and the acoustic analysis of voice samples confirmed the results of the video laryngoscopy. Following treatment with rabeprazole, the typical LPRD lesions on the laryngeal mucosa diminished to a large extent, and the vocal function of the larynx was much improved. Therefore, LPRD should not be overlooked in the treatment of dysphonic patients. Another objective assessment of the voice improvement is acoustic analysis of voice samples that will confirm the VHI subjective results.

CONCLUSION

LPRD causes severe voice disorders, globus pharyngeus sensation, and frequent coughing. Esophagoscopy supplemented with a biopsy of the esophageal mucosa can be a suitable method to prove GERDs occurrence. Video laryngoscopy is superior in the diagnosis of LPRD and correlates very well with the esophageal mucosa specimens' histological findings. Combining these procedures are supposed to be a very successful method in the diagnostics of GERD and especially LPRD. Rabeprazole proved to be very useful in the treatment of LPRD. Subjective and objective voice assessment methods can demonstrate an improvement by the end of the 2-month therapy. LPRD appears to have a substantial adverse influence on voice quality and can be an important overlooked cause in patients with voice disturbance.

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Original Article

Study of Clinical and Radiological Presentation of Cerebral Venous Thrombosis and its Outcome – A Prospective Study

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Abstract

Introduction: Cerebral venous thrombosis is now recognized as a common cause of young stroke with increased incidence in Asian countries, significantly more prevalent in postpartum females in southern India. Diverse manifestations such as diffuse encephalopathy, focal localizing deficits, migrainous headache, seizures, and psychiatric symptoms make early clinical diagnosis difficult.

Aim: The objective of this study was to analyze the diverse clinical and radiological presentation of cerebral venous thrombosis and its correlation with the outcome of the patient.

Methods: A total of 40 patients with the diagnosis of cerebral venous thrombosis were recruited from general medicine and neurology ward in a tertiary care hospital and were interviewed, examined regarding clinical presentation and radiological investigation was collected.

Results: In our study group, cerebral venous thrombosis (CVT) was more prevalent in females (62.5%) than males. Postpartum was the most common associated risk factor (40%) and headache (92.5%) being the most common clinical presentation followed by seizures, vomiting, visual disturbances, and focal deficits. Transverse sinus (77.5%) was the most common involved sinus followed by superior sagittal sinus (52.5%).

Conclusion: Postpartum incidence of cerebral venous thrombosis is highlighted with significance in our study. Involvement of deep cerebral veins, the extension of thrombus up to internal jugular vein, the involvement of multiple venous channels, the patient presented with coma, and presence of frank massive intracerebral hemorrhage were associated with poor outcome in our study. Knowledge about diverse clinical features spectrum in CVT and factors associated with a poor outcome can help us in early diagnosis, reducing the mortality and morbidity among patients.

Key words: Cerebral venous thrombosis, Magnetic resonance venogram, Outcome

INTRODUCTION

Cerebral venous thrombosis (CVT) refers to occlusion of venous channels in the cranial cavity, including thrombosis of dural venous sinuses or the smaller feeding cerebral veins. CVT is more prevalent among young to middle-aged people and is more common in females.[1-4] It is a potentially life-threatening condition requiring early clinical suspicion and prompt treatment. Although most of the patients have an excellent outcome if treated early and appropriately, delayed diagnosis is often possible due to the broad clinical spectrum of symptoms, varied initial presentation, obscuring of symptoms and signs by the underlying disease like meningitis, and normal findings in neuroimaging.

In addition, there exists a vast difference in predisposing factors, presentations, therapeutic options, and outcome of cerebral venous thrombosis among developed and developing countries. For example, the International Study

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on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) 3 reported obstetric CVT in only 20% of cases compared to reports from Mexico and India, which report a much higher frequency.[5,6]

Similarly, CVT incidence is uncertain since it has a wide range of clinical manifestations.[7] However, recently, Panagariya *et al.*[8] reported that 17% of all strokes and half of all strokes in young people are due to CVT. In certain studies, CVT incidence was higher in South Asia and the Middle East.[9,10] Most studies from India have reported many cases; hence, the incidence in India is not as rare as assumed earlier. In India, CVT accounts for 10–20% of young strokes.[10] However, no well-designed large-scale epidemiologic study on CVT has been conducted in South Asia, where it is comparatively frequent.

Aim

The aim of the study was as follows:

1. To analyze the various clinical presentation of cerebral venous sinus thrombosis.
2. To study the radiological characteristics of cerebral venous sinus thrombosis patients and correlate with their clinical presentation.
3. To analyze the various factors contributing to the outcome in cerebral venous thrombosis patients.

MATERIALS AND METHODS

This prospective study was done in the Department of Neurology at Thoothukudi Government Medical College Hospital, Tamil Nadu. All patients attending neurology outpatient department and admitted in the hospital diagnosed with cerebral venous sinus thrombosis from November 1, 2019, to October 31, 2020, were recruited in this study.

All patients included in this study are more than 18 years of age, who satisfy the inclusion criteria, with a confirmed clinical and radiological diagnosis of cerebral venous thrombosis. Patients <18 years of age, who are unwilling to participate in this study, with inconclusive radiological findings to support cerebral venous thrombosis diagnosis are excluded from this study.

A questionnaire was prepared, and all patients included in this study were interviewed and thorough clinical examination of these patients was performed after getting informed written consent. The patients or relatives were asked about the risk factors, presenting symptom, and associated symptoms in detail. Radiological investigations such as computed tomography brain and magnetic resonance imaging (MRI) brain with MR venogram are done, and detailed reports were collected. Treatment history of patients and duration of hospital stay were noted. Association of clinical symptoms, signs of cerebral venous thrombosis patients, and their corresponding radiological features are compared and analyzed with those patients' outcome through statistical analysis.

RESULTS

In this study, 40 patients with the diagnosis of cerebral venous thrombosis were included. Among them, 75% of patients were <40 years old, with the disease more particularly predominant in 21–30 years of age group (40.5%) [Figure 1]. In our study group, CVT was more prevalent in females (62.5%) than males (37.5%) [Figure 2].

Most of the patients presented with headache (92.5 %), being the most common symptom. Others presenting symptoms are seizures (77.5%), vomiting (55%), visual disturbances (50%), focal neurological deficits such as hemiparesis (22.5%), acute confusional state (2.5%), and quadriparesis (2.5%) in descending order, respectively [Figure 3].

Among the prevalent risk factors in our study group, the most common was pregnancy (postpartum CVT) which

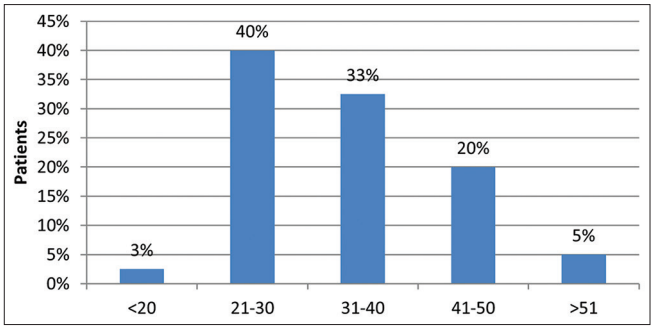

Figure 1: Age distribution of cerebral venous thrombosis

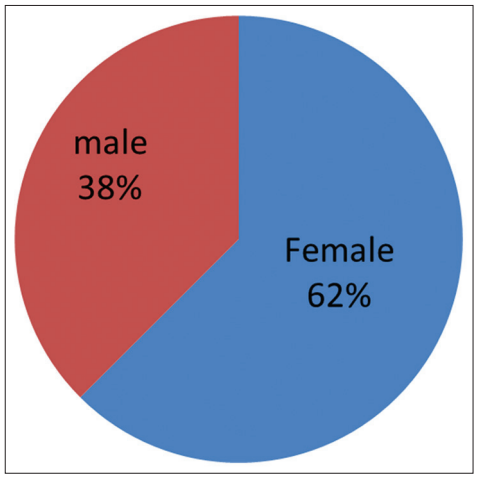

Figure 2: Gender distribution of cerebral venous thrombosis

accounts for 40% of cases. The second most common associated risk factor in our study group is alcoholism (30%), followed by diabetes mellitus (10%), OCP use (5%), diarrhea with dehydration (2.5%), connective tissue disorder (2.5%), and idiopathic causes (10 %), respectively [Figure 4].

Among our study group, 30% of patients presented with an altered level of consciousness, and 25% of patients had papilledema changes in fundus examination. Among higher mental function examination, 2 patients (5%) had aphasia. Furthermore, one patient had bilateral lateral rectus palsy due to raised intracranial pressure, and one patient with cavernous sinus thrombosis had ptosis, paresthesia over face (5th cranial nerve involvement), and 3rd and 4th nerve palsy. Moreover, in our study group, 35% of patients had hemiparesis and 1 (2.5%) patient had quadriparesis.

In our group, 15% of patients had hemorrhage in CT brain itself. In our study group, transverse sinus (77.5%) was the common involved dural venous sinus in MR venogram, followed by sigmoid (55%), superior sagittal sinus (52.5%) [Figures 5 and 6], straight sinus (32.5%), inferior sagittal sinus (10%), and petrosal sinus (10%). Four (10%) patients had deep cerebral veins involvement such as internal cerebral vein, deep vein of Galen, and cortical veins and 2 (5%) patients had thrombus extending to the internal jugular vein, and 1 (2.5%) patient presented with cavernous sinus thrombosis.

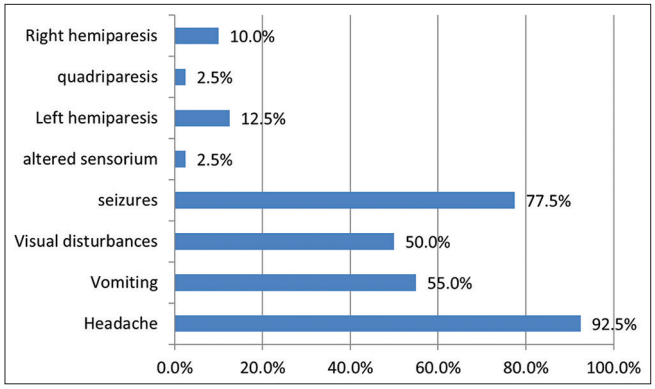

Figure 3: Clinical presentation spectrum of cerebral venous thrombosis in our study population

In MRI, 13 patients (32.5%) did not have any parenchymal changes. Ten patients (25%) had parenchymal edema, 17 (42.5%) patients had a frank intracerebral hemorrhage, and 3 patients (7.5%) had infarct with diffusion restriction among our study population [Figures 7 and 8].

All patients were treated with anticoagulants, antiepileptic drugs, anti-edema measures, supportive iv fluid supplementation, warfarin diet, and physiotherapy. Coagulation profile was monitored and INR was maintained between 2 and 3. Nearly all (38 patients – 95%) recovered while 2 patients (5%) died due to involvement of multiple sinuses, extensive intracerebral hemorrhage, and extension of thrombosis up to internal jugular vein or involvement of deep cerebral veins [Figure 9].

DISCUSSION

Cerebral venous thrombosis (CVT) is considered an uncommon cause of stroke and its incidence is much less common than cerebral arterial thromboembolism.[10] However, in India, CVT accounts for 10–20% of young strokes.[11] The clinical features are diverse; hence, CVT is more challenging to diagnose than other types of stroke.

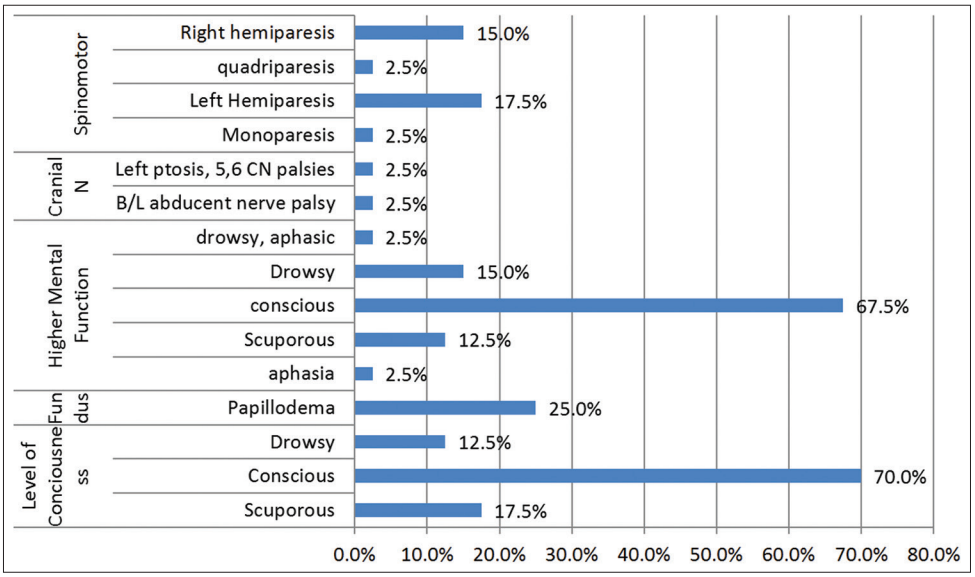

Figure 4: Clinical findings in our study group

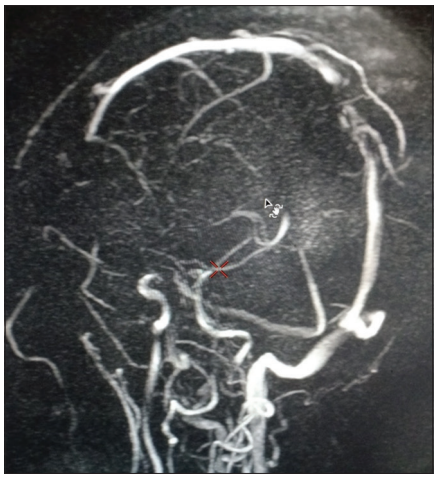

Figure 5: Mid superior sagittal sinus thrombosis in a postpartum female

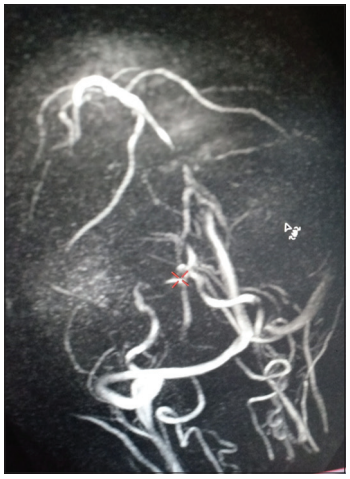

Figure 6: Mid superior sagittal sinus thrombosis

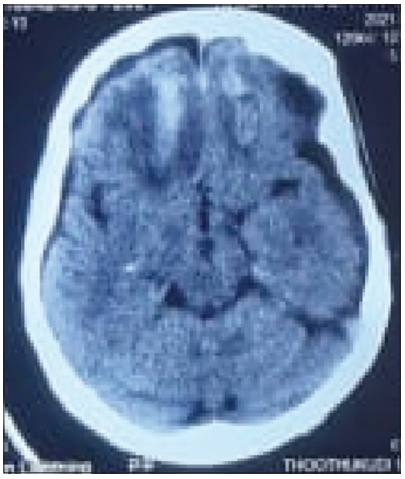

Figure 7: Bilateral frontal hemorrhage in a case of superior sagittal and bilateral transverse sinus thrombosis

Most patients have an excellent outcome if treated early and appropriately.

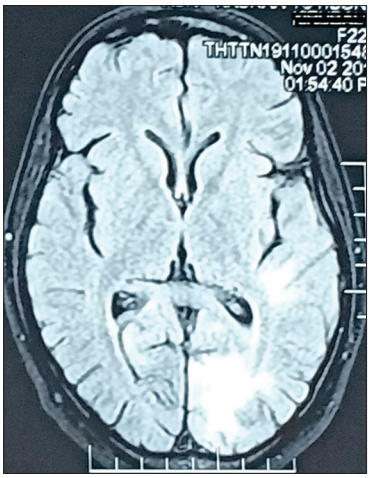

Figure 8: The left parietooccipital T2/FLAIR hyperintensities without diffusion restriction in a postpartum female with the left transverse sigmoid straight sinus thrombosis

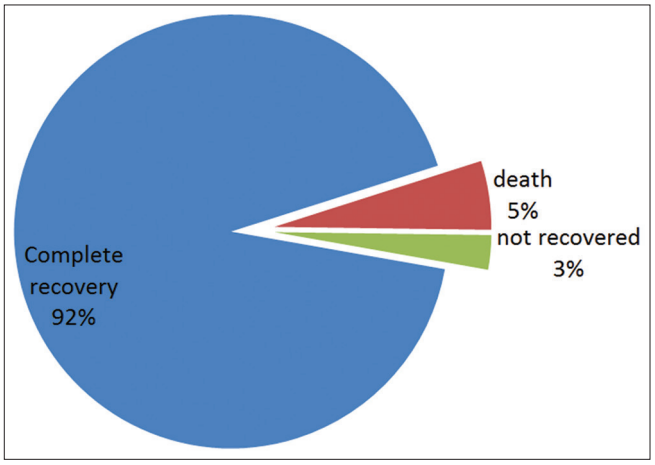

Figure 9: Outcome in our study group

Cerebral venous thrombosis is more common in the younger age group in contrary to arterial stroke. In our study population, it is more prevalent in <40 years age group (75%) comparable with Khaladkar *et al.* (57.5%).[12] It is more prevalent in females in our study population (62.5%), which is in accordance with Ameri and Bosser *et al.*[13] and Ferro *et al.*[14] This female preponderance may be due to risk factor pregnancy, puerperium (40%) and OCP use (5%) which contributed to the occurrence of CVT in our study group which is in accordance with the study by Banakar *et al.*[15] (56.25%, 9.37%) and in contrary to the study by Ferro *et al.* (15%).[14]

Cerebral venous thrombosis causes varied clinical features due to two pathophysiologic mechanisms. First, thrombosis of cerebral veins or sinuses results in increased venular and capillary pressure. As local venous pressure continues to raise, decreased cerebral perfusion results in ischemic injury and cytotoxic edema, disruption of blood–brain

Table 1: Correlation of risk factor with outcome of CVT in our study group

CVT	Outcome			Total	*P* value
	Complete recovery	Death	Not recovered		
Alcoholic	19	1	1	21	<0.0001
-/high platelet count	1	0	0	1	
Connective tissue disorder	1	0	0	1	
Postpartum	15	1	0	16	
Total	36	2	1	39	

barrier leads to vasogenic edema, and venous and capillary rupture culminates in parenchymal hemorrhage.

Second, obstruction of cerebral sinuses may also result in decreased cerebrospinal fluid absorption, which usually occurs through arachnoid granulation into the superior sagittal sinus. Thus, thrombosis of cerebral sinuses not only increases venous pressure but also impairs CSF absorption and ultimately leads to increased intracranial pressure. Increased intracranial pressure aggravates venular and capillary hypertension and leads to parenchymal hemorrhage, vasogenic and cytotoxic edema.[16] Experimental animal data suggest that vasogenic edema occurs earlier in venous stroke than in arterial stroke and cytotoxic edema is far less common in venous stroke.[17]

Hence, most patients in our study presented with headache, probably due to increased intracranial pressure (92.5%). Similar results were found in various studies by Daif *et al.* (82%),[18] Banakar *et al.* (82.7%),[15] Narayan *et al.* (94.4%),[19] and Halesh *et al.* (95%).[20]

Seizures were the second most common presenting feature (77.5%), whereas it is 60% in studies by Barinagarrementeria *et al.*[21] and 48% in the study by Einhaupl *et al.*,[22] and papilledema was seen in 25% of patients comparable with studies by Einhaupl *et al.* (27%).[22]

Among our study group, altered level of consciousness was seen in 30% of patients probably due to postictal confusion which is in accordance with the studies by Banakar *et al.* (54 %)[15] and in study by Barinagarrementeria *et al.* (63%).[19] Motor deficits were seen in 42.5% of patients in our study population according to 48% in a study by Halesh *et al.*[20] and 56.9% in a study by Stolz *et al.*[23]

Involvement of deep cerebral veins is associated with more catastrophic focal motor neurological deficits, and it correlates significantly in our study group ($P < 0.0001$).

The transverse sinus (77.5%) was the most common in our study in contrast to superior sagittal sinus being the most common sinus involved in many studies by Daif *et al.* (85%)[18] and Ameri and Bousser *et al.*[13] (72%). Sigmoid (55%) and superior sagittal sinus (52.5%) are the second most commonly involved sinus in our study population either alone or with other sinuses. Three patients in our study group had isolated superior sagittal thrombosis (7.5%), whereas the rest of the patients (90%) showed thrombosis involving multiple venous sinuses (2.5% cavernous sinus thrombosis).

Table 2: Correlation of venous channels involvement with outcome of CVT

Venous channels	Outcome			*P* value
	Complete recovery	Death	Not recovered	
SSS				
Negative	17	0	1	0.259
Positive	19	2	0	
ISS				
Negative	33	2	0	0.024
Positive	3	0	1	
Transverse				
Negative	7	1	0	0.187
Positive	29	1	1	
Sigmoid				
Negative	17	1	0	0.631
Positive	19	1	1	
Straight				
Negative	25	1	0	0.407
Positive	11	1	1	
Petrosal				
Negative	33	2	1	0.024
Positive	3	0	0	
DCV				
Negative	33	1	1	0.274
Positive	3	1	0	
Others				
CAV	1	0	0	0.169
IJV	1	1	0	
Negative	34	1	1	

In our study population, 95% showed complete recovery, which is contrary to studies by Banakar *et al.*[15] (44.3% had poor outcome). Moreover, among risk factors prevalent in our study population, puerperium correlates significantly with the incidence of cerebral venous thrombosis ($P < 0.0001$). Other risk factors such as chronic alcoholism and OCP use does not correlate

Table 3: Correlation of radiological features with outcome of CVT

MRI brain	Outcome			Total	*P* value
	Complete recovery	Death	Not recovered		
Non-specific findings	3	0	0	3	0.579
Edema	8	0	0	8	
Hemorrhage	15	2	0	17	
Normal	10	0	1	11	
Total	36	2	1	39	

significantly with CVT prevalence (P = 0.592, 0.972, respectively) [Table 1]. One patient was diagnosed with connective tissue disorder (SLE) after the occurrence of CVT in our study group.

Moreover, while comparing imaging findings with the outcome, the involvement of superior sagittal sinus, deep cerebral veins, an extension of thrombus up to internal jugular vein, and multiple extensive venous channels involvement were associated with poor outcome but it does not correlate significantly with death in our study due to small number of deaths in our study group (P = 0.259, 0.274, and 0.169, respectively) [Table 3]. In contrast, involvement of straight sinus was associated with poor outcome in a study by De Bruijn *et al.*[24] Moreover, the occurrence of frank intracerebral hemorrhage at presentation also predicts poor outcome yet significant correlation was not found in our study population due to same reason of small number of deaths deaths (P = 0.579) [Table 2].

CONCLUSION

Cerebral venous thrombosis, due to its broad spectrum of clinical presentation, might be confused with other pathologies, and hence, the diagnosis may get easily missed or delayed. The clinical picture can vary from headache to coma. CVT should be suspected when a young adult presents with stroke, particularly in the absence of vascular risk factors. Likewise, peripartum CVT is the leading risk factor in our setting, thus enforcing the importance of suspecting CVT in every peripartum female with neurological symptoms. Importantly, CVT should always be suspected whenever imaging of the brain shows hemorrhagic infarct, especially in non-arterial territories.

Although the outcome of CVT is in general good if promptly diagnosed and treated, the predictors of poor outcome and death such as involvement of deep cerebral veins, presentation with coma, or frank intracerebral hemorrhage in our study group may help us to provide extra vigilance in case of at-risk patients.

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Original Article

Fetal Foot Length as a Biometric Parameter in Estimation of Gestational Age

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Abstract

Introduction: Sonographic fetal measurements provide information about fetal age and growth. Accurate knowledge of gestational age is important for several reasons. The timing of chorionic villus biopsy in the 1st trimester, genetic amniocentesis in the 2nd trimester, and timing of elective induction/cesarean delivery in the 3rd trimester depends on GA. This study assesses the efficacy of fetal foot length measurement as a biometric parameter in predicting gestational age.

Aim: This study aims to evaluate the role of fetal foot length as a biometric parameter in estimation of gestational age along with conventional parameters biparietal diameter, femur length, and abdominal circumference in normal pregnancy.

Materials and Methods: Pregnant women of gestational age 15–40 weeks attending the antenatal outpatient department and inpatient department during the second and third trimesters in Kilpauk Medical College, Chennai, were assessed clinically and other conventional. USG parameters were measured. After getting approval from the ethical committee, Kilpauk Medical College, the study was done with patient consent. A thorough obstetric examination was made and documented. Under the guidance of expert sonologist, USG estimation of BPD, FL AC, and foot length were done. The role of fetal foot length measurement as a reliable parameter in predicting gestational age and conventional parameters was then analyzed and reported.

Results: Fetal foot length correlates well with the conventional parameters such as biparietal diameter, femur length, and abdominal circumference. The correlation coefficient [R] of fetal foot length is 0.9827, 0.9563, and 0.9791 with BPD, FL, and AC, respectively. The correlation of fetal foot length with conventional parameters is statistically significant with $P < 0.0001$ in all of the above three correlations.

Conclusion: Fetal foot length is a reliable biometric parameter in predicting accurate gestational age on which obstetric decisions can be made with precision for a better perinatal outcome.

Key words: Fetal foot length, Gestational age, Ultrasonographically age estimation

INTRODUCTION

Introduction of sonography to obstetrics by Donald *et al.* in 1958 is now regarded as one of the modern medicine's significant milestones. Recent advances such as color Doppler and high-intensity transducers have made diagnosis more precise. A technologically advanced four-dimensional ultrasound allows the clinician to acquire a single volume that can be reformatted at any orientation. A subsequent meta-analysis published by Bucher and associates based on four randomized controlled studies with data on 15,935 women found that perinatal mortality rate was much reduced in the group of patients subjected to routine USG.[1] Accurate knowledge of gestational age is essential for a number of reasons. The diagnosis of preterm labor and the characterization of pregnancy as postdated depend mainly on accurate fetal age calculation. Knowledge of fetal age can be critical in distinguishing normal from pathologic fetal development. Many sonographic parameters have been proposed for estimating GA in the 1st, 2nd, and 3rd trimesters. The American College of Radiology, American Institute of USG in Medicine, and American College of Obstetrics and Gynaecology, parameters recommended for accurate gestational age estimation is biparietal diameter (BPD), abdominal circumference (AC), and femoral length (FL).[1]

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Crown rump length (CRL) is the best biometric parameter in the first trimester; biparietal diameter closely correlates in mid-trimester abdominal circumference forms an important measure in evaluating appropriate growth; and femur length is the best in the evaluation of skeletal dysplasia. The use of more than 1 predictors is shown to have improved accuracy of estimates. We should take into account various epidemiological factors in assessing growth pattern. Specific growth profile charts are recommended for every different community.

In the second trimester, the biparietal diameter, head circumference, transcerebellar diameter, abdominal circumference, femur length, and other long bones are also useful. In 1987, MERCER *et al.* did the study of fetal foot length measurement to predict accurate fetal age. They concluded that fetal foot length was a reliable parameter for determining gestational age and was particularly useful in hydrocephalus conditions anencephaly, skeletal dysplasia, or short limb dwarfism.[2] In normal scenarios, we depend on MSD, CRL, BPD, HC, and FL for a conclusion. However, in exceptional situations such as macrocephaly/microcephaly, limb dysplasia,[2] engaged head in late pregnancy, in cases of fetal growth retardation difficulty, may arise and hence we need alternative reliable parameters like fetal foot length which is a relatively simple technique, performed easily in everyday practice with good reliability. In 1920, Streeter *et al.* proposed that fetal foot could be used to estimate fetal age.[3] Shalev *et al.* proposed the same agreement between fetal foot length and prediction of gestation.[4] Our study assesses the validity of fetal foot length in the accurate estimation of fetal gestational age.

Aim

This study aims to evaluate the role of fetal foot length as a biometric parameter in estimation of gestational age along with conventional parameters biparietal diameter, femur length, and abdominal circumference in normal pregnancy.

MATERIALS AND METHODS

This prospective study was conducted in pregnant women of gestational age 15–40 weeks as assessed clinically and measuring other conventional USG parameters attending the antenatal outpatient department and inpatient department during the second and third trimesters in our Kilpauk Medical College, Chennai. Patients with structural anomalies, oligohydramnios, and multiple pregnancies were excluded from the study. After getting approval from ethical committee, Kilpauk Medical College, the study was done with patient consent, detailed menstrual (whether the patient is sure of her menstrual dates or not, LMP), previous obstetric, and past medical and surgical history were taken. Patients general condition was examined. Vitals such as pulse rate, blood pressure, and the temperature were checked. Cardiovascular and respiratory systems were examined. A thorough obstetric examination was made. All routine investigations were done as a part of the antenatal examination. Obstetric ultrasound examination was done in patients included in study USG estimation of BPD, FL AC, and foot length done and documented.

RESULTS

This scatter diagram shows that foot length in mm taken along Y-axis and biparietal diameter taken along X-axis showed a significant correlation of 0.9827 with a significant $P < 0.0001$ [Figure 1].

This scatter diagram shows foot length in millimeters plotted in Y-axis and femur length in millimeters plotted in X-axis showing a positive coefficient of correlation of 0.9563 which is a significant thing with $P < 0.0001$ this further helps to consider fetal foot length measurement as a reliable biometric parameter in assigning fetal age [Figure 2].

This scatter diagram depicting foot length in Y-axis and abdominal circumference in X-axis also had good correlation of 0.9761 with a significant $P < 0.0001$ [Figure 3].

This scatter diagram studying the linear correlation coefficient of 0.9955 comparing lower limit of foot length with standard biparietal diameter [Figures 4 and 5].

The previous two scatter diagrams measuring correlation between foot length and femur length which already showed a significant linear relationship the upper and lower range limits of both parameters when compared also shows good measurement of agreement with a statistically significant, $P < 0.001$, the 95% confidence interval being not very wide [Figure 6].

This scatter diagram depicting foot length in mm lower range is analyzed for its correlation with upper and lower limit of abdominal circumference and found to have significant correlation with a correlation coefficient of 0.9855 with $P < 0.0001$ which is statistically significant [Figures 7 and 8].

DISCUSSION

Fetal foot length can be a reliable measurement in fetal age prediction in the case where conventional parameters are of less reliability. Biparietal diameter cannot be accurate in places of abnormal head shapes like microcephaly or macrocephaly. Head circumference cannot be used in assessing gestational age in cases of dolichocephaly.[5]

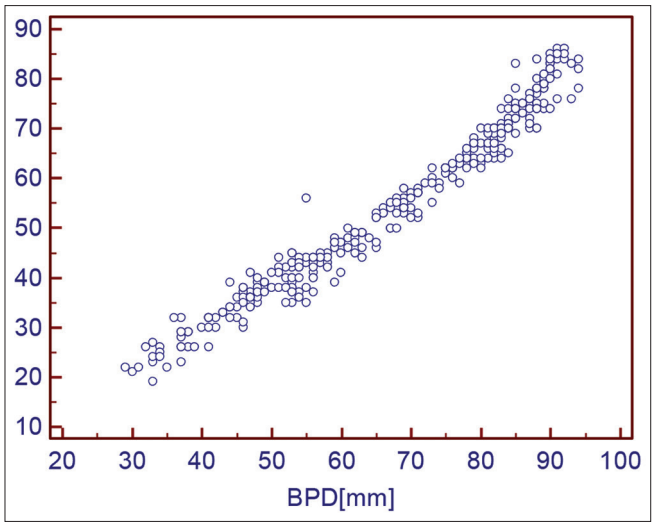

Figure 1: Correlation of foot length with BPD in estimation of GA

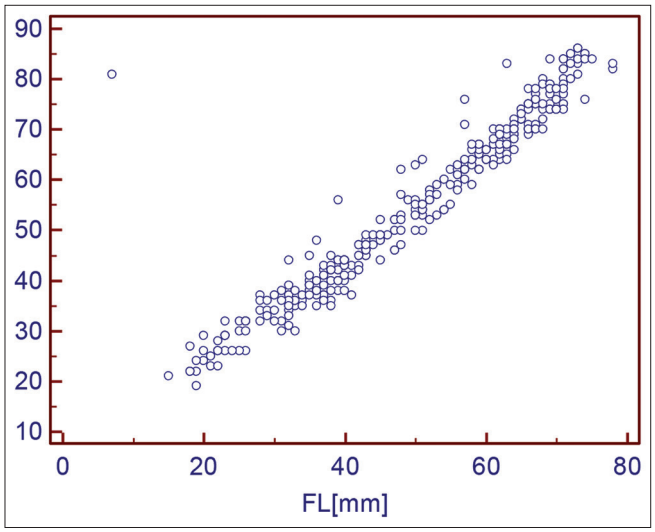

Figure 2: Correlation of foot length with FL in estimation of GA

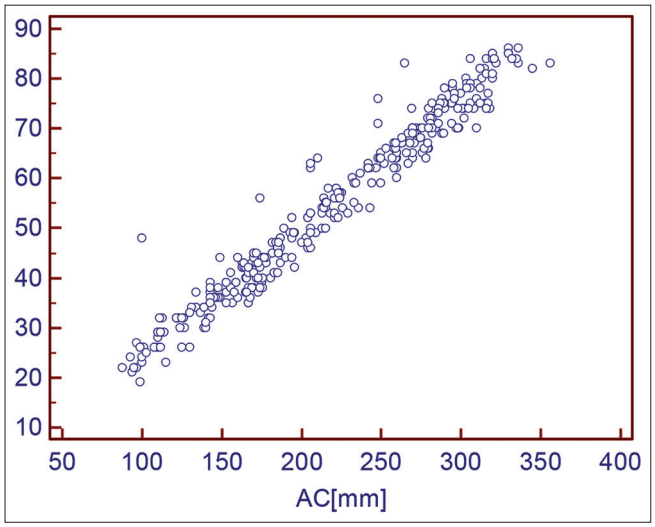

Figure 3: Correlation of foot length with AC in estimation of GA

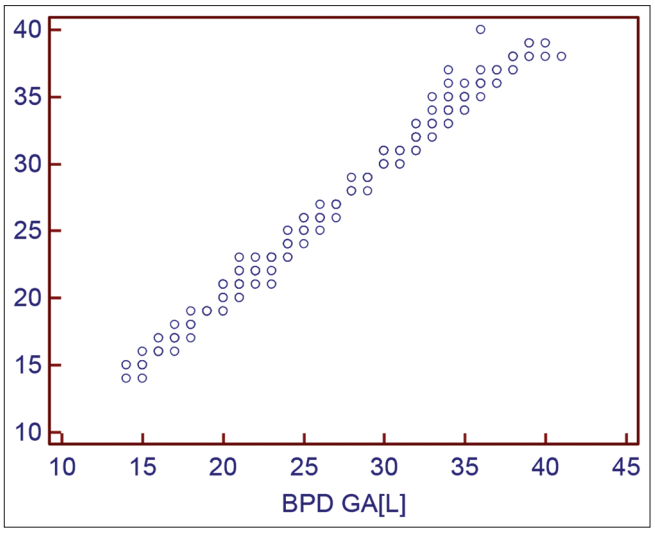

Figure 4: Correlation of foot length [L] with BPD [L] in estimation

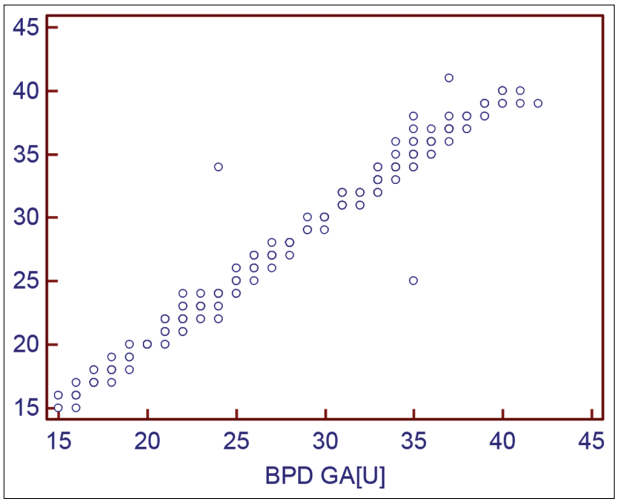

Figure 5: Correlation of foot length [U] with BPD [U] in estimation of GA

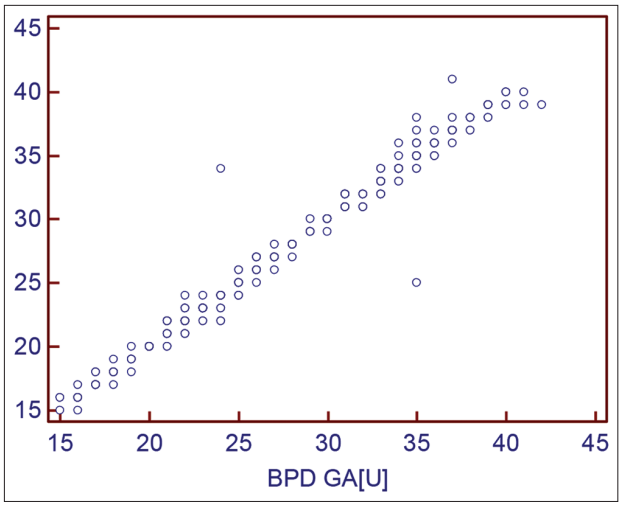

Figure 6: Correlation of foot length [L] with FL [L] in estimation GA

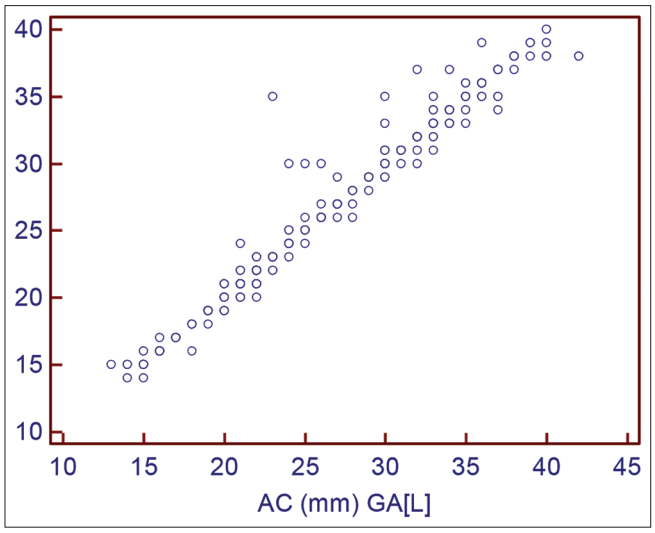

Figure 7: Gestation age: Foot length [L] correlation with AC [L] in estimation GA

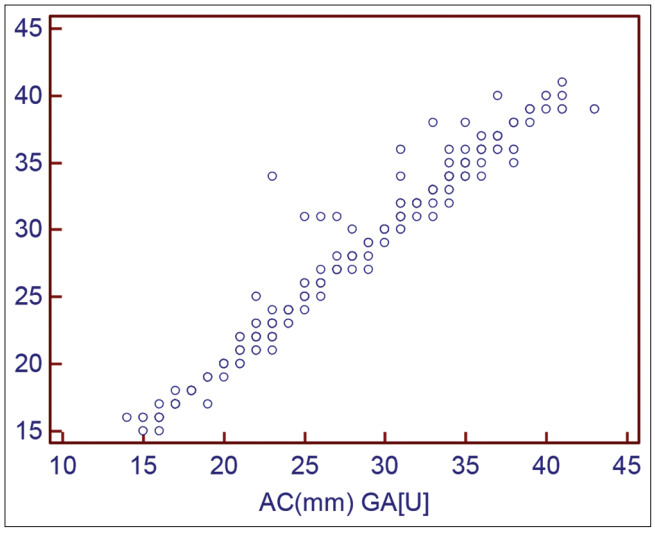

Figure 8: Correlation of foot length [U] with AC [U] in estimation of GA

The long bones length measurement studied in fewer studies, failed to predict gestational age of growing fetus accurately because the skeletal limb dysplasia is virtually affecting most of the bones.[6] It cannot be depended even in conditions like short limb dwarfism. In case of anencephaly, a neural tube defect occurs due to deficiency of folate and other antiepileptic therapy; there is the absence of skull calvaria, then it is difficult to ascertain gestational age by conventional methods such as biparietal diameter or head circumference or transcerebellar diameter/occipitofrontal diameter. In such situations, along with other traditional parameters, femur length and abdominal circumference fetal foot length can be a good reliable parameter.[6,7]

When choosing a single best fetal parameter to assess the period of gestation, there is little biologic variation. Each study claims one parameter to be more reliable than other conventional parameters. Using multiple biometric parameters as in my study, the accuracy of fetal age estimation can be greatly improved which helps in a very great way to make appropriate clinical decisions regarding timing of termination of pregnancy, and induction of labor to minimize maternal morbidity, mortality, and improved perinatal outcomes which is our ultimate goal.[8] The use of multiple parameters also reduces the effects due to biologic phenomenon or a technical error that occurs in a single measurement. It is also known from various studies to ascertain gestational age that random errors get reduced with multiple parameter measurement rather than a single parameter in the estimation.[9]

About 20% of antenatal women do not have reliable dates,[4] may cycle irregular due to various reasons, it is our duty to estimate gestational age in those individuals also to decide on the timing of delivery the mode of induction and to decide risk–benefit ratio in certain high-risk pregnancies such as preeclampsia, overt diabetes, heart diseases, Rh isoimmunization, and so on. Among my study group, there were 43 patients with irregular cycles whose biometric parameters were analyzed to find whether fetal foot length measurements can predict accurate gestational ages. The analysis showed that it reliably predicts fetal age with a correlation coefficient of 0.98 and a significant $P < 0.0001$. From this study, it is evident that fetal foot length reliably helps in the accurate estimation of gestation even in patients with irregular cycles.

CONCLUSION

Fetal foot length measurement is a reliable parameter in predicting gestational age along with conventional parameters biparietal diameter, femur length, and abdominal circumference. Fetal foot length measurement reliably predicts gestational age in antenatal women with irregular menstrual cycles. Fetal foot length can be influenced by fetal growth abnormalities. This study implies that the fetal foot length measurement has a limited role in growth abnormalities. Foot length is more accurate in ascertaining period of gestation in the second trimester than the third trimester. Further studies are required in the cohort of IUGR to establish the role of foot length in gestational age prediction. To conclude, fetal foot length is a reliable biometric parameter in predicting accurate gestation age on which obstetric decisions can be made with precision for a better perinatal outcome.

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Original Article

Study of Patients with Vitamin D Deficiency and Hypocalcemia in Hypothyroidism – An Observational Study

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Abstract

Introduction: Vitamin D deficiency is linked with predisposition to various autoimmune diseases, including multiple sclerosis (MS), rheumatoid arthritis (RA), diabetes mellitus (DM), inflammatory bowel disease, and systemic lupus erythematosus (SLE). The primary action of Vitamin D is the regulation of calcium and phosphorus homeostasis. Several studies demonstrated a relationship between Vitamin D deficiency, autoimmune thyroid disorders, and thyroid cancer.

Aim: The aim of this study was to study the association of Vitamin D deficiency and hypocalcemia in hypothyroidism.

Materials and Methods: This observational study was conducted in the Department of General Medicine, Government Medical College, Pudukkottai, in patients with Hypothyroidism. Venous samples were collected from all patients. The quantitative determination of 25 (OH) Vitamin D and serum Ca^{2+} was done using spectrophotometer method. Levels of TSH, T3, and T4were estimated using fluorescence array.

Results: Out of 50 patients, 38 were female, and 12 were male. The mean age was 42.38 ± 7.12 years. Mean duration of Hypothyroidism was 5.12 ± 2.48 years. The mean value of TSH was 8.48 ± 2.14 mU/L, T3 value was 0.88 ± 0.09 ng/mL, T4 value was 6.72 ± 1.02 mIU/mL, 25-hydroxy Vitamin D 14.28 ± 1.44 ng/ml, and calcium was 7.41 ± 0.38 mg/dl.

Conclusion: Hypothyroidism patients had 25-hydroxy Vitamin-D deficiency and hypocalcemia, hence screening for Vitamin D deficiency and serum calcium levels for all hypothyroid patients warranted.

Key words: 25-Hydroxy Vitamin-D, Hypocalcemia, Hypothyroidism, Vitamin D

INTRODUCTION

Vitamin D is a steroid produced by the skin, and it aids in the regulation of expression of various genes.[1] The primary action of Vitamin D is the regulation of calcium and phosphorus homeostasis, deficiency of Vitamin D has become a common health problem in the general population. Vitamin D insufficiency has been linked to various morbidities such as cardiovascular disease, insulin resistance, fatty liver disease, type2 diabetes and its complications, infections, and cancer.[2] Apart from a skeletal metabolism role, Vitamin D has been recognized as both an exogenous and an endogenous player in endocrinopathies such as type 1 and type 2 diabetes mellitus, adrenal diseases, and polycystic ovary syndrome.[3,4] It has also been linked to several autoimmune disorders, including autoimmune thyroid disorders (AITD).[5,6]

Hypothyroidism, the exchangeable pool of calcium, and its turnover rate are reduced, reflecting decreased bone formation and resorption. Hypothyroidism levels of parathyroid hormone are often slightly increased with some degree of resistance to its action, and 1,25(OH)2D (dihydroxyvitamin D) are also increased.[7]

Aim

The aim of this study was to study the association of Vitamin D deficiency and hypocalcemia in hypothyroidism.

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MATERIALS AND METHODS

This observational study was conducted in the Department of General Medicine, Government Medical College, Pudukkottai in patients with hypothyroidism. Structured questionnaires were administered to them to obtain demographic information including age, gender, and BMI. Venous samples were collected from all patients. The quantitative determination of 25 (OH) Vitamin D and serum Ca^{2+} was done using spectrophotometer method. Levels of TSH, T3, and T4were estimated using fluorescence array. A serum 25 –OH vitamin D level of 0–20 ng/ml was considered as deficient, level 21–29 ng/ml was considered insufficient, and > 30 ng/ml was considered sufficient. Serum calcium levels were done using dpectrophotometer method.

RESULTS

In this study, 50 patients with hypothyrdism were included, 38 were female, and 12 were male. The mean value of age among 50 patients were 42.38 ± 7.12 years. Duration of hypothyroidim in this patients was 5.12 ± 2.48 years. Mean value of thyroid parameters in this patients was, T3 0.88 ± 0.09 ng/mL, T4 6.72 ± 1.02 mIU/mL, and TSH 8.48 ± 2.14 mU/L. In this patients, 25-hydroxy Vitamin D level was 14.28 ± 1.44 ng/ml and calcium level was 7.41 ± 0.38 mg/dl [Tables 1-3].

Table 1: Gender distribution

Gender	Number of patients
Male	12
Female	38

Table 2: Age distribution

	Mean value
Age	42.38±7.12years

Table 3: Diseases parameters

Diseases parameters	Mean value
Duration of hypothyroidism	5.12±2.48 years
TSH	8.48±2.14 mU/L
T3	0.88±0.09 ng/mL
T4	6.72±1.02 mIU/mL
25-hydroxy Vitamin D	14.28±1.44 ng/ml
Calcium	7.41±0.38 mg/dl

DISCUSSION

Thyroid diseases are the most prevalent in endocrine disorders.[8,9] There are 7–95% females and 1–2% males across the world with variable thyroid conditions.[10] In previous decades, Vitamin D deficiency was considered virtually non-existent in the Indian population as India lies in the tropical area.[11] However, nowadays, various studies have revealed that 50–90% of the Indian population is deficient in Vitamin D due to inadequate dietary intake of Calcium.[12]

Vitamin D deficiency has been recognized as a global health problem. Due to its role in the homeostasis of blood calcium level and decreasing the risk of rickets fractures in children, osteoporosis, and osteomalacia in old age, Vitamin D is of immense importance in our body. Besides its classical role in skeletomuscular functions, Vitamin D has been recently identified as a deeply involved factor in both innate and adaptive immunity.[13] "Secosteroid Hormone," the biologically active form of vitamin D, essential for bone and mineral homeostasis, has also been shown to have immunoregulatory and anti-inflammatory effects. A low level of Vitamin D in blood either due to less absorption or deficient intake was associated with several autoimmune conditions, such as type 1 diabetes mellitus, Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. It has recently been shown that the population in tropical areas is even at high risk of Vitamin D deficiency. This may be attributed to lifestyle-changing behaviour. The best Vitamin D status indicator is the serum concentration of 25(OH)D, which reflects Vitamin D produced cutaneously and obtained from food and other supplements.[13] This 25(OH)D has a half-life of about 15 days in the circulation.

Majority of the patients in our study were female. This finding was similar to that of Mackawy *et al.*[14] Fida,[15] and Naeem *et al.*[16] They stated that serum Vitamin D levels were significantly more decreased in females than males. This was in accordance with our finding. Although several authors have reported that Vitamin D levels did not differ significantly between males and females.[14,17,18] Furthermore, the present study showed that Vitamin D and calcium serum levels were significantly lower in hypothyroid patients than the controls. A significant positive association was recorded between Vitamin D and calcium levels in both groups. Husein *et al.*[14] found a similar finding in their study.

In a study conducted by Koch *et al.*[19] in North Indian population of Meerut, 53.94% of subjects were Vitamin D deficient. A study conducted by Bhardwaj *et al.*,[20] 56% of the hypothyroid subjects, in whom Vitamin D levels were below 20 ng/ml. There were only 10% of subjects who had sufficient levels of Vitamin D.

CONCLUSION

Hypothyroidism patients had 25-hydroxy Vitamin D deficiency and hypocalcemia, hence screening for Vitamin

D deficiency and serum calcium levels for all hypothyroid patients warranted.

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Original Article

Validation of Laboratory Risk Indicator for Necrotizing Fasciitis Scoring System for Diagnosis of Necrotizing Fasciitis in Patients Presenting with Soft-Tissue Infections

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Abstract

Introduction: Necrotizing fasciitis (NF) is a rapidly progressive inflammatory infection of the fascia, with secondary necrosis of the subcutaneous tissues. The speed of spread is directly proportional to the thickness of the subcutaneous layer.

Aim: The aim of this study was to validate the Laboratory Risk Indicator for NF (LRINEC) scoring system for the diagnosis of necrotizing fasciitis among patients presenting with soft tissue infections.

Materials and Methods: Patients presenting with signs and symptoms of NF admitted were counseled to investigate and treat NF and its complication. Using a semi-structured pro forma to collect information on patients' characteristics and covariates of soft-tissue infections.

Results: Out of 100 patients, 93 patients had lower limb cellulitis and seven patients had upper limb cellulitis. While comparing the HPE with the LRINEC scoring system, 18 patients were true positive for NF, 76 patients true negative for NF, two patients were false positive, and 4 patients were false negative. In my study, the sensitivity is 81.82%, specificity is 97.44%, the positive predictive value is 90.00%, the negative predictive value is 95.00%, and accuracy is 94.00%.

Conclusion: LRINEC scoring system has a better positive predictive value in identifying the onset of NF and risk strategizing of the patients with severe soft-tissue infection. There is a statistically significant association between diabetes mellitus and the severity of the risk.

Key words: Laboratory risk indicator for necrotising fasciitis score, Necrotising fasciitis, Peripheral vascular disease, Systemic inflammatory response syndrome

INTRODUCTION

Necrotizing fasciitis (NF) causes significant inflammation and destruction of skin, deep fascia and soft tissues, toxemia typically caused by Streptococcus pyogenes bacteria, but sometimes due to mixed infections such as anaerobes, coliforms, and Gram-negative species.[1]

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The disease is prevalent in patients with age, smoking, diabetes, immunosuppression, malnutrition, obesity, steroid therapy, and HIV. Diabetes and injury are a significant factor/cause of precipitation – 80%.

The patient is highly toxic and then the skin is painful, red and gangrenous as blood supply is depleted. Fascial gangrene is usually wider than the involvement of clinically evident skin.[2]

Diagnosis is challenging due to the absence of clear skin signs to distinguish NF from certain soft-tissue diseases such as cellulitis. Since decades, this illness has baffled physicians.[3]

While understanding NF pathophysiology continues to improve, this disease's mortality indicates surprisingly high with recorded death rates ranging from 6% to 76%.

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Prompt diagnosis and prompt surgical intervention are the only factors in reducing morbidity and mortality in patients with NF.[4]

This can be easily understood: The longer the lag, the higher the loss of tissue and sepsis, resulting in increased deaths.

One of the main reasons for the growing high mortality rate of patients with NF today is the lack of early diagnosis and management of the condition due to the absence of clinical symptoms of the skin early in its formation.[5]

This needs an easier-to-follow scoring system and a high positively and negatively predictive value that is price-effective.

One possible scoring system developed by Wong Et is the Laboratory Risk Indicator for NF (LRINEC) scoring system in 2005, the predictive value was 92.0% positive and the predictive value was 96.0% negative.[6]

Therefore, I would like to check this scoring system in our patients and, if it was found to have similar predictive values, it would be a blessing for developing countries like India, where disease mortality ranges from 7% to 76% and where resources are also scarce.[7]

Aim

The aim of this study was to validate the LRINEC scoring system for the diagnosis of NF among patients presenting with soft-tissue infections.

MATERIALS AND METHODS

The study data were obtained from patients hospitalized with a provisional diagnosis of NF on clinical evaluation and who are admitted at Tirunelveli Medical College and Hospital, Tirunelveli. Patients presenting with signs and symptoms of NF admitted during January 2018 to September 2019 at Tirunelveli Medical College and Hospital were counseled for Necrotizing investigation and treatment fasciitis and its complication.

Exclusion Criteria

The following criteria were included in the study:

- Patients below 15 years or above 75 years of age.
- Patients who have received antibiotic treatment in the last 48 h or have received a minimum of three doses of antibiotics before presentation.
- Patients who have undergone surgical debridement for present episode of soft-tissue infections.
- Patients with burns or furuncles with no evidence of cellulitis.

Assessment of Parameters

All consenting patients with NF would be clinically examined after history taking and then subjected to blood investigations as follows:

- C-reactive protein
- Hemoglobin
- Glucose
- Creatinine
- Sodium
- Total white cell count
- Tissue for histopathology
- Patients presenting with symptoms suggestive of soft-tissue infections will undergo clinical examinations and the above mentioned investigations.
- Using a pre-tested semi-structured pro forma cum quantitative checklist, which will collect information on characteristics and covariates of soft-tissue infections.
- LRINEC scoring system will be applied to each of the study subjects. The confirmatory diagnosis for necrotizing fascitis will be done with histopathology for all patients, irrespective of the result of the LRINEC scoring system [Table 1].

RESULTS

Out of 100 patients studied, 65 patients belong to the age group of 41–60 years and it is evident that the incidence of soft-tissue infection increases in this age group. Out of 100 patients, 72 patients were male and 28 were female. Out of 100 patients, 93 patients had lower limb cellulitis and seven patients had upper limb cellulitis [Figure 1]. Diabetes mellitus (DM) is being responsible for most cases of soft-tissue infection in my study group around 46% followed by trauma – 18%,

Table 1: LRINEC scoring scale

Laboratory parameter	LRINEC points
C-reactive protein (mg/l)	
<150	0
≥150	4
Total white blood cell count (µl)	
<15	0
15–25	1
>25	2
Hemoglobin (g/dl)	
>13.6	0
11–13.5	1
<10.9	2
Sodium (mmol/l)	
≥135	0
<135	2
Creatinine (mg/dl)	
≤1.6	0
>1.6	2
Glucose (mg/dl)	
≤180	0
>180	1

LRINEC: Laboratory risk indicator for necrotizing fasciitis.

bites – 14%, CKD – 12%, PVD – 7%, and unknown – 3% [Table 2]. In LRINEC score variables, Hb <13 gm% is being the most common biochemical abnormality that is seen in necrotizing fascitis around 77 patients followed by RBS – 55, creatinine – 39, CRP – 34, sodium – 16, and WBC – 15. Out of 100 patients, 80 patients had LRINEC score <5 and 20 patients had LRINEC score > or = 6 [Figures 2 and 3]. HPE group shows, out of 100 patients, 78 had cellulitis, 22 had necrotizing fasciitis [Figure 4]. While comparing the HPE with the LRINEC scoring system, 18 patients were true positive for NF, 76 patients true negative for NF, 2 patients were false positive, and 4 patients were false negative. In my study, the sensitivity is 81.82%, specificity is 97.44%, the positive predictive value is 90.00%, the negative predictive value is 95.00%, and accuracy is 94.00% [Figure 5].

Table 2: Etiological distribution

Etiology	Frequency	Percent
Diabetes mellitus	46	46.0
Trauma	18	18.0
Bites	14	14.0
CKD	12	12.0
PVD	7	7.0
Unknown	3	3.0
Total	100	100.0

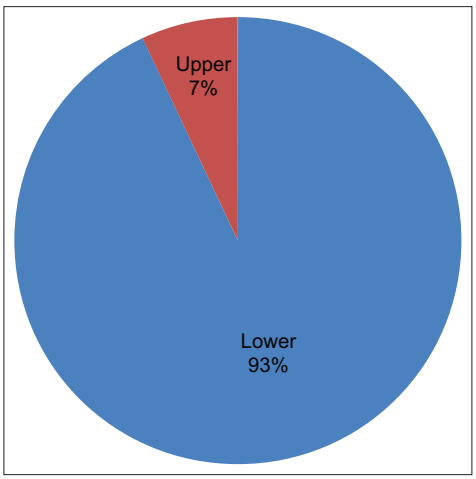

Figure 1: Limb distribution

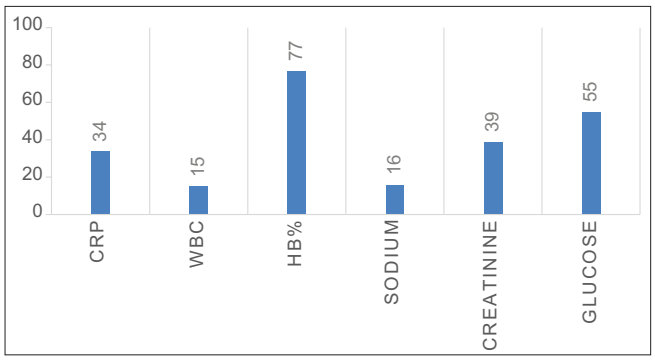

Figure 2: Score distribution

DISCUSSION

NF is a rare but rapidly progressive, devastating soft-tissue necrosis that usually involves fascia and subcutaneous tissues with a significant hospital morbidity and mortality.

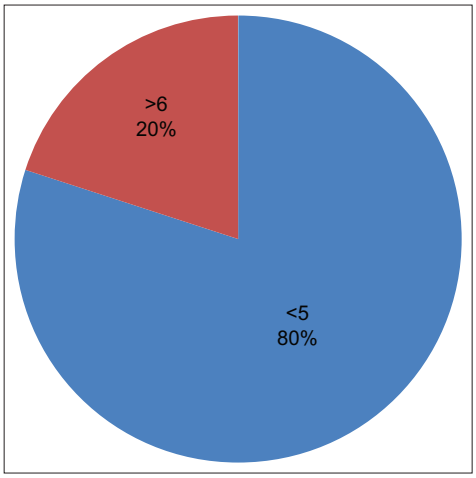

Figure 3: Laboratory risk indicator for necrotizing fasciitis <5 and >6

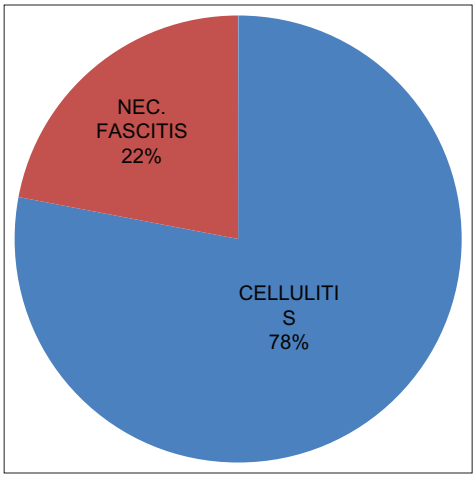

Figure 4: HPE group

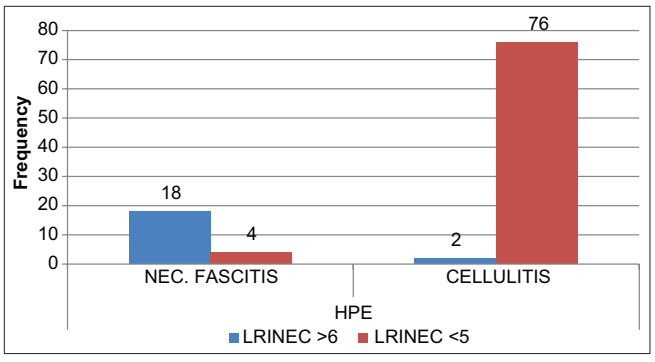

Figure 5: Cross-tabulation of laboratory risk indicator for necrotizing fasciitis versus HPE

It has been estimated that 13 per million of populations are hospitalized each year for NF, of which the mortality is 20–30%.

The mortality rate could reach up to 100% in the absence of proper and timely diagnosis and treatment.

The most common risk factors for NF are DM, immunodeficiency diseases, illicit drug use, and malnutrition.

This kind of infection can occur with a trivial wound or often without any provocation.

Early diagnosis, aggressive serial debridement, broad-spectrum antibiotics, and multidisciplinary critical care approach are vital to attain favorable outcomes in NF patients.

The LRINEC is a scoring system driven from six routinely performed laboratory tests and used initially to early distinguishing NF from the other severe soft-tissue infections.

Multiple studies have evaluated the usefulness of LRINEC for early detection of NF and found that it could be used to identify and classify NF patients into differing categories, thus facilitating the adequate management of hospital resources.

However, few studies have observed an association between LRINEC scoring values and outcomes in patients with NF.

Chao *et al.* in Korea (2012) Studies show that the average LRINEC rating of 2 or higher was 71% adaptive, 83% precise, and 85% positive predictive, with an 11.9-fold increased risk for the presence of NF ($P < 0.0001$).[8]

Su *et al.* in Taiwan (2002–2005) shows patients with a LRINEC score of more than or equal to 6 have a higher mortality rate as well as an amputation rate.[9]

Corbin *et al.* in France (2008) shows that in patients with LRINEC score above 6, the complication rate was higher than, in patients with a score below 6.[10]

Swain *et al.*, in UK, overall mortality was 3 out of 15 patients. The median LRINEC score in all deaths was 9.0 (range: 6–13).[11]

Colak *et al.* in turkey (2013), the mean number of debridement and LRINEC score was higher in the non-surviving group.[12]

There is always a need to find a simplified bedside, validated, and rapid tool to early stratify patients with a potential life-threatening illness.

The present study aims to evaluate the role of LRINEC score as a diagnostic tool for in-hospital outcomes in patients with NF.

CONCLUSION

LRINEC scoring system has a better positive predictive value in identifying the onset of NF and risk strategizing of the patients with severe soft-tissue infection. There is a statistically significant association between DM and the severity of the risk. At the end of my study, the LRINEC scoring has been validated and found to have an accurate diagnostic tool in predicting the outcome of patients with soft-tissue infections.

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Original Article

Role of Alvarado Score in Diagnosing Acute Appendicitis: A Prospective Observational Study

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Abstract

Introduction: Acute appendicitis is a surgical emergency, which is associated with morbidity and mortality occasionally, so accurate diagnosis and timely intervention is needed. Therefore, the present study is conducted to evaluate the Alvarado scoring system in diagnosing acute appendicitis and its correlation with histopathology.

Aim: The aim is to study the effectiveness of Alvarado score in diagnosing acute appendicitis.

Materials and Methods: The study population consists of 100 patients admitted in casualty with suspicion of acute appendicitis. The Alvarado scoring system scores the severity of acute appendicitis and the patients were divided into three groups and managed according to the severity.

Results: Group A had 54 patients with scores 7–10 and considered acute appendicitis and taken for emergency appendicectomy. Out of 31 patients in Group B, 18 were conservatively managed, and 13 were diagnosed with acute appendicitis and operated. Out of 15 patients in Group C, two were operated, and 13 were managed conservatively.

Conclusion: In this study, the sensitivity, specificity, and positive predictive value were 89.66%, 59.52%, and 75.36%, respectively. Younger age group is predominant. This scoring system is a dynamic one, allowing observation and reevaluation of the clinical picture. Its value in decision-making is high both in males and females. Its application improves diagnostic accuracy and considerably reduces the negative laparotomy rate.

Keywords: Abdominal pain, Acute appendicitis, Alvarado score, Appendicectomy

INTRODUCTION

Diagnosis of appendicitis is usually easy, but it is still difficult to diagnose acute appendicitis mainly because of the challenge we face while diagnosing acute appendicitis on clinical grounds.[1]

Acute appendicitis is a common cause of surgical emergency that needs to be diagnosed with accuracy to reduce the morbidity and mortality associated with it.[1,2]

Acute appendicitis is seen in day-to-day practice in the emergency department as one of the most common surgical emergencies.

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It can sometimes confuse the practitioners by its presentation. The delay in early diagnosis or failure in early diagnosis may happen many times. This may lead to disease prognosis. This will further lead on to increase in morbidity as well as occasional mortality in the patient.[3]

Although there are many recent trends in investigatory modalities, diagnosis of acute appendicitis is still in a mystery, leading to an increase in operative indication for the patient due to the fear of complication followed by it.

There is an increase in the negative appendicectomy rate of about 20% seen in the literature.[4,5]

Therefore, Alvarado developed a scoring system in 1986 to diagnose acute appendicitis, thereby reducing the rate of negative appendicectomy without causing an increase in morbidity and mortality.

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Alvarado described the scoring system in 1986. Alvarado A in 1994 later modified it by taking one laboratory finding of the scoring system.[6]

The Alvarado scoring system in patients with the pre-operative clinical diagnosis of appendicitis has been useful in the early diagnosis of acute appendicitis as demonstrated by various studies and helped reduce the incidence of negative appendicectomies without increasing the morbidity and mortality.[6]

Aim

This study aims to study the effectiveness of Alvarado score in diagnosing acute appendicitis.

MATERIALS AND METHODS

A prospective observational study was done in the Department of General Surgery, Tirunelveli Medical College. One hundred patients suspected of acute appendicitis were included in the study. Patients satisfying the inclusion and exclusion criteria were enrolled in the study. Inclusion criteria: All patients presenting with the right iliac fossa pain. Exclusion criteria: Pain >5 days duration, appendicular lump/mass, features of peritonitis, features of intestinal obstruction, history of trauma to the right iliac fossa, patients with genitourinary complaints, pregnant females, patient with the previous history of any abdominal surgeries, patient not willing for surgery, and age <12 years were excluded from the study. Depending on individual presentation of signs and symptoms, a score was calculated for each suspected appendicitis case from eight values (based on Alvarado scoring system).

- Total score 7–10, these patients were considered to have acute appendicitis and patients were prepared and emergency appendicectomy was done
- Total score 5–6, these patients were considered equivocal, and hence, they are observed by conservative management. If the general condition and the patients' symptoms were improved, means patients were discharged with the advice to return if the symptom recurs. If the patients developed severe pain and the total score increased, they had to be taken up for surgery
- Total score 1–4, these patients were considered to have either less severe appendicitis or some other. Such a group of patients were managed symptomatically and then discharged. They were also advised to come if the symptoms recur
- Histopathological examination of the appendix specimen was done.

RESULTS

In the present study, we had 100 cases out of which 43 were male and 57 were female. In this study, 69 were operated for acute appendicitis, including 31 female patients and 38 male patients. The number of patients was highest in the age group of 13–20 years (57%) followed by 21–30 years (27%). The least was in the age group for more than 50 years (4%). Most of the patients were of a younger age group. The younger age group is predominant and the incidence peaks in the age group of 13–30 and decreases with age [Table 1].

Majority of the patients had tenderness in the right iliac fossa as the predominant symptom followed by anorexia and migrating pain [Table 2].

Out of 69 patients operated, 30 were taken up for open appendicectomy and 39 underwent laparoscopic appendicectomy [Table 3].

There were 11 cases of appendicular perforation and all those patients had Alvarado score of 7–10 and none of them was missed by Alvarado score. Only two cases were missed by Alvarado scoring and they had increased scores on reassessment and were operated. Out of 69 patients operated, ultrasonogram findings showed acute appendicitis in 32 patients, probe tenderness in RIF in 26 patients, and normal in 11 patients. Alvarado score was in favor of acute appendicitis even though ultrasonogram was normal in some patients [Table 4].

Table 1: Distribution of age group

Age group (year)	Frequency	Percent
<20	57	57.0
21–30	27	27.0
31–40	9	9.0
41–50	3	3.0
>50	4	4.0
Total	100	100.0

Table 2: Distribution of symptoms

Features	Score	Frequency	Percentage
M	1	67	67.0
A	1	72	72.0
N	1	55	55.0
T	2	98	98.0
R	1	23	23.0
E	1	43	43.0
L	2	65	65.0
S	1	42	42.0

Table 3: Cross-tabulation of Alvarado score with management

Alvarado score	Management	
	Surgery	Conservative
7–10	54	0
5 and 6	13	18
1–4	1	14

In this study, the sensitivity, specificity, and positive predictive value were 89.66%, 59.52%, and 75.36%, respectively [Table 5 and Figure 1].

DISCUSSION

Acute appendicitis is the most common acute surgical condition of the abdomen. Over the past 100 years, the morbidity and mortality rates related to this condition have markedly decreased. This is because of the recognition of the deleterious effects of appendiceal perforation. Thus, an aggressive surgical treatment strategy involving early operation with acceptance of a high negative appendicectomy rate of 15–30% is universal. Although the negative appendicectomy has negligible mortality, it has associated morbidity rate of 10%. The diagnostic accuracy of clinical assessment of acute appendicitis varies from 50% to 80%. The clinical diagnosis is especially difficult in the very young, the elderly, and the women of reproductive age group.[7,8]

Table 4: Cross-tabulation of Alvarado score with HPE

Alvarado score	HPE			Total
	Conservative	Acute appendicitis	Perforated appendix	
7–10	0	43	11	54
5 and 6	18	13	0	31
1–4	14	1	0	15

Table 5: Area under the curve

AUC	Std. error[a]	*P*-value	Asymptotic 95% confidence interval	
			Lower bound	Upper bound
0.947	0.020	0.0001	0.908	0.986

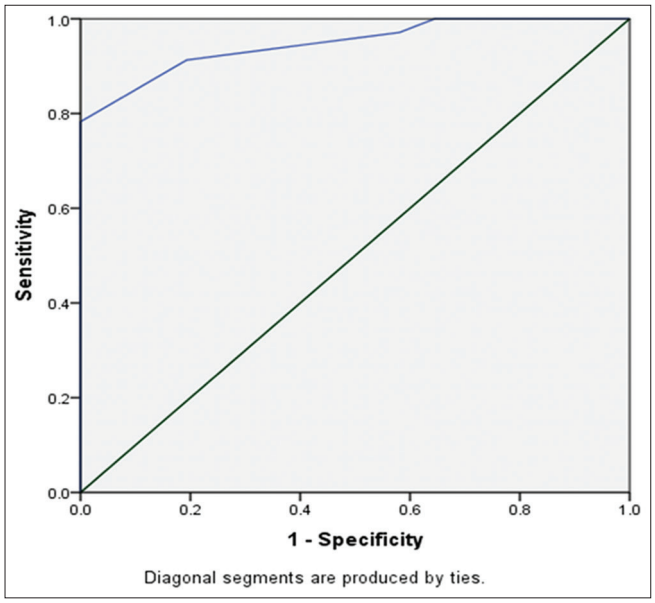

Figure 1: ROC curve

Appendicitis still poses a diagnostic challenge and many methods have been investigated to reduce the removal of a normal appendix without increasing the perforation rate. Radiological methods such as ultrasonography and computed tomography and an invasive procedure like laparoscopy are all methods that have been investigated previously. Many diagnostic scores have seen advocated but most are complex and difficult to implement in a clinical situation. The Alvarado score first described in1988, is a simple scoring system. Good clinical acumen remains the mainstay of correct diagnosis of appendicitis.[6] It is a scoring system that can be instituted easily in the outpatient setting and a cheap and quick tool to apply in the emergency room Alvarado score is an objective assessment of the right lower quadrant pain. The score indicated >7 which indicates high probability of acute appendicitis. Practically speaking, it is equivalent to one's degree of clinical suspicion. Therefore, this scoring system was used to reach the clinical diagnosis. It was considered that using the scoring system to make the clinical diagnosis would allow uniformity as more than 1 senior surgical resident was involved in making the decision. Men accounted for 41% and women 59% of the study group. The maximal incidence of acute appendicitis was found between the ages of 21 and 30, comparable with the literature. In the study by Ohmann *et al.*[9] and Arian *et al.*,[10] the negative appendicectomy rate was 14.3% and 16.1%. In this study, all the 11 cases of perforative appendicitis had scored 7 or more and were operated, thereby giving 0% missed perforation rate. The two cases which were missed initially came back with increased severity of symptoms and had a higher Alvarado score on reevaluation and were operated. The probable reason for the two false negatives in our study may be the very early stage of acute appendicitis they might have presented initially, thereby hindering the clinical diagnosis.

In this study, the sensitivity, specificity, and positive predictive value were 89.66%, 59.52%, and 75.36%, respectively. This study also shows that the Alvarado scoring system application in diagnosing acute appendicitis can provide a high degree of positive predictive value and thus diagnostic accuracy. This study's positive predictive value is comparable with the studies done by Kalan *et al.*,[11] Malik *et al.*,[12] and Owen *et al.*[2] who reported 87.5%, 85.3%, and 87.4%, respectively.

CONCLUSION

The Alvarado scoring system in patients with the pre-operative clinical diagnosis of appendicitis has been

useful in the early diagnosis of acute appendicitis as demonstrated by various studies and helped reduce the incidence of negative appendicectomies without increasing the morbidity and mortality.

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Original Article

Study of Major Pediatric Ophthalmic Complications in Consanguineous Marriage

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Abstract

Introduction: Consanguineous marriage is the practice of marrying close blood relatives, commonly cousins; it is customary in many cultures worldwide. The risk of congenital disabilities is higher because there is a greater chance of two related individuals sharing a common harmful gene and passing it on to the child.

Aim: This study aims to assess various types of eye disorders in children to establish a relationship between consanguineous marriage and eye disorders in their offspring.

Materials and Methods: To ensure scientific and clinical relevance on this matter, individual's data of patients were obtained through a questionnaire which comprised information, including the diagnosis of the eye disorder, age of parents at the time of marriage, number of pregnancies, type of delivery, ratio and degree of consanguineous and non-consanguineous marriages, birth complication, and birth weight. Data entry and analysis were performed using SPSS version 16.0. The quantitative data were presented using the arithmetic mean, standard deviation and analyzed using one-way ANOVA.

Results: Consanguineous marriage among affected patients was significantly higher in our study group [59%] and represented as 41%, 32%, and 27% in the first cousins, one and a half cousins, and second cousins, respectively. Four types of eye diseases such as squint, glaucoma, cataract, and retinitis pigmentosa were prominently found. Most of the affected children and their parents belong to rural background, mostly being less educated, which indicated the lack of knowledge about the impact of consanguineous marriage.

Conclusion: This work suggests that premarital genetic, social counseling, and mass media efforts are needed to increase public awareness about genetic risks associated with cousin marriage. A further study is crucial to do a detailed survey for a long time; the affected person's DNA should be isolated to do chromosome mapping and gel documentation to identify the affected gene.

Key words: Consanguinity, Eye diseases, India, Pediatric

INTRODUCTION

Consanguinity has been defined as the marriage or union between people of the same blood, which has decreased heavily in most developed countries. However, marriages between biological relatives have remained common in developing countries.[1] Consanguinity is common, especially in people originating from the Middle East, the northern parts of Africa, and large parts of Asia.[1] Such marriage makes offspring susceptible to various types of genetic disorders. The highest consanguineous marriage rates in South India are usually reported in traditional rural areas and among the poorest and least educated groups.[2] In many communities in India, the first preference is to get married within the family. Intracommunity and consanguineous marriages are still more common, and it has been so for centuries. Much of India, particularly South India, practiced endogamy or marriages within the community for centuries. In many communities, preference has been given to uncle-niece marriages and between cousins (mother's brother's child and father's sister's child). In Tamil Nadu and Andhra Pradesh, usually one in two marriages in the rural areas is consanguineous.[3] Pregnancy

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outcomes such as abortions, stillbirths, congenital anomaly, and neonatal and infant deaths were more common in consanguineous marriages.[3]

Aim

This study aims to assess various types of eye disorders in children to establish a relationship between consanguineous marriage and eye disorders in their offspring.

MATERIALS AND METHODS

A prospective study was conducted in an ophthalmic hospital in South India. Children between the age groups of 2 and 12 years are considered in this survey. Data were collected through a survey method using a standard questionnaire form. It includes the questionnaire regarding the patient's history. It was obtained from the children's parents, such as the type of delivery of affected children as to whether it is a normal delivery or cesarean, if cesarean, was there any complication during pregnancy. Then marriage details were also collected regarding whether they had a consanguineous marriage or non-consanguineous marriage. The high degree of consanguinity shows the high level of sharing the genes between the parents. The maternal age during pregnancy was also noted. Finally, the baby and its siblings' numerical order details whether the siblings are having any complications related to the affected child's disease and the birth weight of the child during the delivery were obtained.

Data entry and analysis were performed using SPSS version 16.0. The quantitative data were presented using the arithmetic mean, standard deviation. The variance analysis (ANOVA) was calculated to check the relationship between maternal age and degree of consanguinity.

RESULTS

Consanguinity marriage is still being practiced in India. It is reported to be more in rural areas when compared to urban areas. For this study, a survey was conducted on 75 children and their parents. The prevalence of consanguinity marriage was significantly higher in most of the study population (59%) [Table 1].

Consanguinity marriages represented 41%, 32%, and 27%, among the first cousins, one and a half cousins, and second cousins, respectively [Table 2]. Significant ($P > 0.05$) correlation was observed between maternal age group and degree of consanguinity [Table 3].

When the family history was analyzed for the prevalence of eye defects, the ratio of frequent occurrences of eye diseases was observed to be high among first cousins. In this current study, we observed that the mother's age during pregnancy plays an important role in disease prevalence. About 46% of the patients' mothers' fall in the age group of 26–30 years [Table 4]. Among consanguineous marriage couples, a delayed pregnancy rate has been observed.

There was no distinguishable difference in the birth weight of affected children, which was mostly normal. The abnormal to normal birth weight is usually considered to be 1.6–3.5 kg, respectively. In this survey, birth weight varied between 2.0 and 2.8 kg which were categorized to be normal [Table 5].

Table 1: The prevalence of consanguinity marriage among patients

Type of marriage	Parents
Consanguinity marriage	44
Non-consanguinity marriage	31

Table 2: The degree of consanguinity

Degree of consanguinity marriage	Number of individuals
Maternal uncle	17
Second cousins	14
Close relatives	17

Table 3: One-way analysis of variance for maternal age and degree of consanguinity

Groups	Sum of squares	df	Mean square	F	Sig.
Between groups	6.400	8	0.800	1.600	0.548
Within groups	0.500	1	0.500		
Total	6.900	9			

AQ6

Table 4: The maternal age during delivery

Age of mother during pregnancy	No. of patients
16–20	4
21–25	27
26–30	33
31–35	11

Table 5: The birth weight of children who had participated in the survey

Birth weight	No. of children
1–1.5	2
1.6–2.0	9
2.1–2.5	27
2.6–3.0	33
3.1–3.5	4

Of the entire study population who had participated in the survey, ocular defects were observed in 40 male children while 35 female children have ocular defects. Of the children affected with ocular defects, 63 children were diagnosed with squint followed by 8 children with cataract, glaucoma and retinitis pigmentosa in 2 patients each. Both esotropia and exotropia squints were observed. Most of the patients were well aware of squint disease, which is identified at an earlier stage.

Child marriage practice was found to be considerably low in the study. The affected children's parents have some awareness about eye diseases such as squint, glaucoma, cataract, and retinitis pigmentosa. In our study, there was a high prevalence of squint in children compared to other ocular diseases. It affected male to a great degree when compared to female.

In our study, normal delivery was observed in 44 patients, while cesarean was observed in 31 patients. Ocular eye defects were observed mostly in children born after cesarean delivery (9 children). In the siblings of the affected children born to consanguineous parents, no ocular disease was reported except in the sibling of one affected child.

DISCUSSION

Consanguineous marriage occurs among Muslims, Christians, and Hindus to a varying degree within each religion's subgroups. The tradition of arranged marriage is the main factor for consanguine marriage. Consanguineous unions are strongly preferred in much of Asia's west and south parts and have both social and economic impacts on the population groups that practice this type of marriage.

In the current study, the influence of consanguinity on the prevalence of visual disorders was examined in patients coming for treatment. The result showed the highest percentage of consanguinity marriage among the parents of affected children. Consanguineous unions increase in prevalence in the states south of the Narmada, with the highest rates reported in Andhra Pradesh, Karnataka, and Tamil Nadu.[4]

In 1993, consanguineous marriage was higher in South India in various society sections, except in Kerala. At that time, in Andhra Pradesh, the percentage of consanguineous marriages was about 36.2. Next to Andhra Pradesh, in Tamil Nadu, there was a more common practice of consanguineous marriage. Overall, the percentage of consanguinity in India was about 12.9. Whereas in 2008, consanguine marriages were considerably reduced and it was about 8.5%.[4]

In 59% of our study population, ocular defects were observed. Of them, 41%, 32%, and 27% were first cousins, one and a half cousins, and second cousins. These results obtained were higher than the results obtained in the study by Shawky *et al.*[5] who reported that the consanguineous marriage was highly significant in 54.4% of the studied group compared to 35.3% in the control group ($P < 0.05$) and consanguineous marriages were represented in 31.4%, 7.1%, 0.8%, 6%, and 9.1% among first cousins, one and a half cousins, double first cousins, second cousins, and remote relatives, respectively.

In the present study, eye-related diseases such as squint, glaucoma, cataract, and retinitis pigmentosa were recorded. Consanguineous marriages are associated with an increased risk for congenital malformations and autosomal recessive diseases, with some resultant increased postnatal mortality in the offspring of the first cousin couple.[6]

Concerning the religious status of affected children, all the parents of the ocular affected children from the Muslim community surveyed were shown to have the consanguineous marriage. The observed results can be correlated with Bittles and Hussain[4] who reported that consanguineous marriage is common in most Indian Muslim communities. It is estimated that globally over 20% of the human population live in communities with a preference for consanguineous marriage, and over 8.5% of all children have consanguineous parents.[4]

In this study, three children from the Christian community had a squint. Their parents were interviewed, and it was found that they were not married consanguinity. However, they said that the prevalence of squint is common among their close relatives. The low number of consanguinity in the Christian community can be substantiated with the low prevalence of consanguine marriages among Kerala people because of the strict avoidance of consanguineous marriage among Christian Syrian members orthodox church.[7]

There is a positive relationship between the higher maternal age of the mother and children's eye diseases. The result is supported by Hornby *et al.*[6] who stressed the importance of maternal age because some disorders increase in incidence with mothers' age.

In this study, consanguineous marriage was seen in 59% of our studied group. This practice is common in South India because many families prefer marriage among first cousins to preserve the family structure, links, and provide social, economic, and cultural benefits. Cousin marriages remain culturally and socially favored and respected in many countries.[8]

Usually, most of the affected population was from rural areas. This condition may be attributed to a lack of knowledge about

the impact of consanguinity. Srinivasan and Mukherjee[2] revealed that the highest consanguineous marriage rates in South India are usually in traditional rural areas and among the poorest and least educated groups. However, close kin marriage is commonplace in Brahmin communities, and it may be strongly favored among major landowning families.[9] These data suggest that premarital genetic, social counseling, and mass media efforts are needed to increase public awareness about genetic risks associated with cousin marriage.

Our results showed that the high degree of consanguineous marriages was among first cousin marriage. The same was also reported among Egypt's general population, where first cousin marriages occurred in 86% of study subjects. The autosomal recessive and multifactorial disorders had the highest consanguinity rate (78.8% and 69.8%, respectively).[2]

The incidence of primary and secondary glaucoma was very low in our study. By the time, glaucoma is diagnosed, a high percentage of them become blind. In consanguineous marriage, genetic and medical disorders are increased in the offspring with time. It is a big challenge for our society to get complete information about their prevalence, risk factors, and control of these disorders.

CONCLUSION

We observed that the rural people showed high levels of consanguinity and are under a high risk of eye-related defects through our work. We suggest that premarital genetic, social counseling, and mass media efforts are needed to increase public awareness about genetic risks associated with cousin marriage. There is also a need for developing policies by the government and work in coordination with NGOs to promote awareness in rural areas about the impact of consanguineous marriages on offspring.

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Original Article

Role of Diabetic Retinopathy Stage in the Outcome of Anti-VEGF Therapy in Macular Edema

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Abstract

Introduction: Diabetic retinopathy is a complication of diabetes and the leading cause of vision impairment. It has been found that vascular endothelial growth factor (VGEF) inhibiting factors will control diabetic macular changes.

Aim: Our study aims to find the effect of the stages of diabetic retinopathy in the outcome of anti-VEGF therapy in macular edema.

Materials and Methods: A retrospective observation study was done in patients with diabetic retinopathy were included. Subjects with ocular diseases other than diabetic retinopathy were excluded from the study. The data on the patient refractive power, ophthalmoscopic findings on the stage of the diabetic retinopathy, the macular thickness as measured by the optical coherence tomography (OCT), and the fundus fluorescein angiography (FFA) findings were noted from the medical records.

Results: A total of 40 patients were included in this study. Twenty-five are male and 15 were female with a mean age of 56 ranging from 43 to 69 years. Forty subjects, 16 subjects belong to the moderate non-proliferative diabetic retinopathy (NPDR) stage. Three subjects had mild NPDR, 13 subjects had severe NPDR, and 8 subjects had proliferative diabetic retinopathy (PDR). The retinal findings included microaneurysm (MA), hemorrhages (HE), neovascularization at the disc (NVD), neovascularization elsewhere (NVE), vitreous hemorrhage (VH), tractional retinal detachment (TRD), and clinically significant macular edema (CSME). The number of cases with high macular thickness has become less post-therapy indicating the decrease in macular thickness with therapy.

Conclusion: There is an improvement in the vision and macular edema with anti-VEGF treatment. It has also been found that the higher the macular edema more efficient the anti-VEGF therapy is.

Key words: Anti-VEGF therapy, Diabetic macular edema, Diabetic retinopathy

INTRODUCTION

Diabetic retinopathy (DR) is a complication of diabetes and the leading cause of vision impairment and blindness among working-age adults. It occurs when diabetes damages the tiny blood vessels in the retina, which is the light-sensitive tissue at the back of the eye. Diabetic retinopathy may lead to diabetic macular edema. The likelihood of developing diabetic retinopathy is related to the duration of the disease. Type 2 diabetes has an insidious onset and can go unnoticed for years. As a result, patients may already have DR at the time of diagnosis. Type 1 diabetics, on the other hand, are diagnosed early in the course of their disease, and they typically do not develop retinopathy until years after the diagnosis is made. The risk of developing retinopathy increases after puberty. Twenty years after the diagnosis of diabetes, 80% of type 2 diabetics and nearly all type 1 diabetics show some signs of retinopathy. While these numbers are eye opening, diabetics can decrease their risk of retinopathy and slow the progression of the disease after it has begun with tight glucose control.[1]

Glucose control also has the added benefit of decreasing the risk for other end-organ complications of diabetes,

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so diabetic patients must be educated on the topic. Time since diagnosis and extent of hyperglycemia is the most significant risk factor for the DR, but other risk factors for development and progression include hypertension, dyslipidemia, smoking, nephropathy, and pregnancy. Diabetic retinopathy involves damage to the retina, the light-sensitive tissue at the back of the eye.[2]

Diabetic macular edema (DMO) which may occur at all stages of diabetic retinopathy (DR) is a severe vision-threatening complication. In most cases, laser treatment does not improve visual acuity. Therefore, research in ophthalmology focuses on the improvement of the prognosis of DMO patients with a drug-based DMO therapy. Vascular endothelial growth factor (VEGF) is considered the most important therapeutic target because this growth factor also is the most potent permeability factor affecting the inner retinal barrier formed by endothelial cells (ECs). Compared to its angiogenic stimulation of proliferation and migration of ECs, the effects of VEGF on permeability have not been studied in all details. *In vitro* investigations on the behavior of primary or immortalized retinal endothelial cells confirmed the key role of VEGF in the regulation of the permeability of the inner retinal barrier. Despite the presence of a variety of other factors found to be elevated in DR, a VEGF disrupted barrier can be completely restored with the VEGF inhibiting ranibizumab and bevacizumab when applied at clinically achievable concentrations. The antibody bevacizumab, but not the antibody fragment ranibizumab, accumulates in both retinal EC and pigment epithelial cells during prolonged treatment. It is not clear that anti-VEGF is the effect in all stages of diabetic retinopathy.[3] Hence, we would like to find the effect of the stage of diabetic retinopathy in the outcome of anti-VEGF in macular edema.

Aim

Our study aims to find the effect of the stage of diabetic retinopathy in the outcome of anti-VEGF in macular edema.

MATERIALS AND METHODS

This retrospective study was conducted in the tertiary ophthalmic hospital at Tirunelveli. The inclusion criteria for selecting the patient records were defined as patients diagnosed with diabetic retinopathy with the macular thickness measured using OCT and FFA done with the detailed documentation of comprehensive eye examination with pre- and post-anti-VEGF treatment. The age group of the subjects ranged from 43 to 69. Both Type I and Type II diabetic patients were included in the study. All stages of diabetic retinopathy were included in the study. We excluded the patients who have any other ocular disease other than diabetic retinopathy.

Patients who had undergone vitrectomy, intravitreal application of glucocorticoids, laser photocoagulation, and VEGF inhibitors in combination with laser were also excluded from the study. Intraocular surgery within 3 months of initiation of anti-VEGF therapy was excluded from the study. The presence of significant media opacity that would limit vision recovery (e.g., significant cataract, VH, and corneal scar), presence of coexisting macular disease (e.g., age-related macular degeneration and vascular occlusive disease), vitreomacular traction as determined by spectral domain OCT, macular ischemia if noted by the treating physician based on fluorescein angiography, previous vitreoretinal surgery (e.g., vitrectomy), and less than 1-year follow-up from initial injection was excluded from the study.[4]

Data extraction was carried out by a single researcher. Visual acuity was extracted from the records for both pre- and post-VEGF therapy. The visual acuity values were the best-corrected visual acuities based on the logarithm of minimal angle of resolution (log MAR).

We extracted the data on the subject's refractive power, ophthalmoscopic findings on the stage of diabetic retinopathy, the macular thickness as measured by the OCT, and the FFA findings.

RESULTS

A total of 40 subjects were included in this study. Twenty-five are male and 15 were female with a mean age of 56 ranging from 43 to 69 years.

In this study, out of 40 subjects with diabetic retinopathy with macular edema was more in the age group 51–60 years (42.50%) and less in the age group ≤ 40 (2.50%) years. The distribution of the number of subjects in the different age groups is listed in Table 1.

Of 40 patients, 2 had Type I diabetes and 38 had Type II diabetes. Overall, the mean metabolic parameters remained relatively stable during the study period. The subjects were at different stages of diabetic retinopathy. The distribution of different stages of DR is plotted in Figure 1.

In this study, out of 40 subjects, 16 subjects belong to the moderate NPDR stage. The background retinal findings included MA, HE, NVD, NVE, VH, TRD, and CSME. The distribution of these findings is plotted in Figure 2.

In this study, out of 40 subjects, clinically significant macular edema is present in all of these patients. Out of

40 subjects, NVD and NVE were present in the same number. In both conditions, it is present in 8 (20%) subjects. MA, HE, and TRD were also present (80%, 77.5%, and 30%, respectively) [Figure 3].

We can see that the number of subjects in the log MAR value 0.00–1.00 (that is the group of best visual acuity increased from 34 to 38) and the number of subjects (that is the group of moderate visual acuity) decreased, indicating that there is an improvement in visual acuity with pre- and post-anti-VEGF therapy [Figure 4]. The intraocular pressure did not have much variation between pre- and post-therapy, as shown in Table 2.

Table 1: Age distribution of subjects

Age in years	No. of subjects	Percentage (%)
≤40	1	02.50
41–50	8	20.00
51–60	17	42.50
61–70	14	35

Table 2: IOP pre- and post-therapy

IOP (mmHg)	No. of subjects	
	Pre-anti-VEGF therapy	Post-anti-VEGF therapy
≤10	2	4
11–20	36	36
21–30	2	0

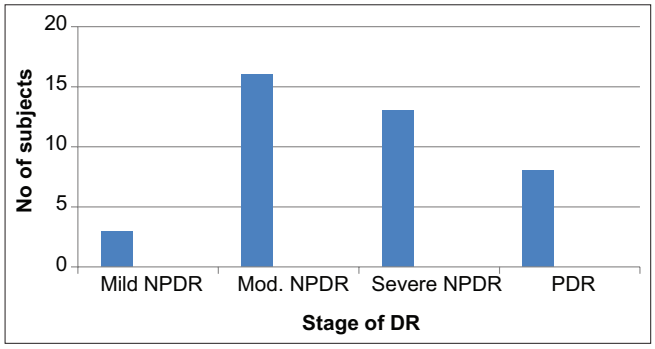

Figure 1: Stages of DR

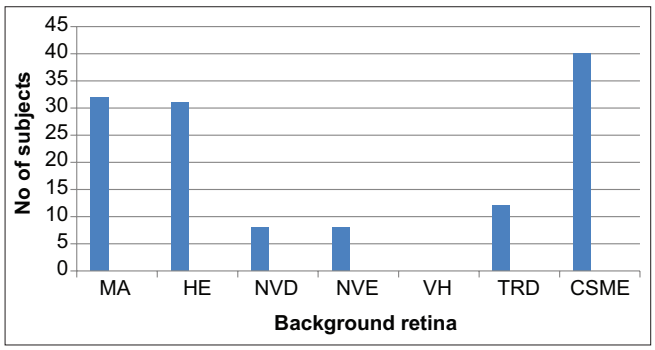

Figure 2: Background retina

As we expect that the macular thickness reduces with the VEGF therapy, we see that the number of cases with high macular thickness has become less post-therapy [Figure 5].

The X-axis was plotted with initial macular thickness and the Y-axis is plotted with the difference in macular thickness between pre- and post-anti-VEGF therapy.

DISCUSSION

Zechmeister-Koss *et al.* analyzed vascular endothelial growth factor inhibitors (anti-VEGF) in the management

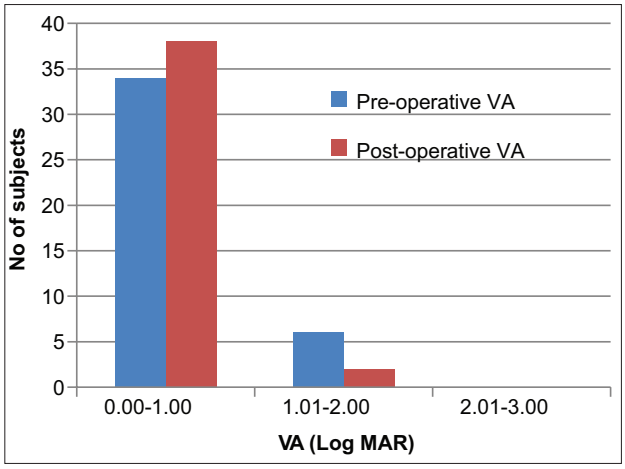

Figure 3: Visual acuity pre- and post-anti-VEGF therapy

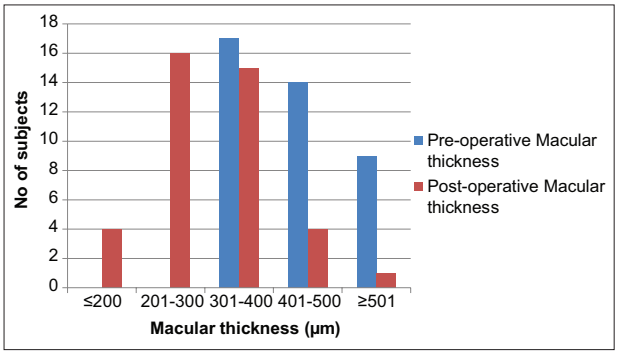

Figure 4: Macular thickness pre- and post-anti-VEGF therapy

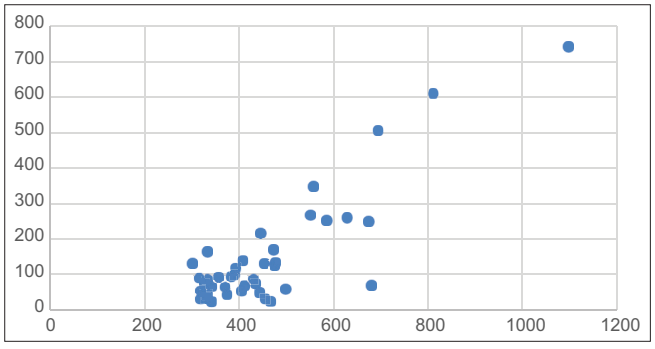

Figure 5: Treatment efficiency versus the amount of macular edema

of diabetic macular edema. Vascular endothelial growth factor inhibitors lead to better clinical outcomes than current treatments in patients with clinically manifest diabetic macular edema which is the leading cause of vision loss in the working-age population in developed countries. In a proportion of patients, VEGF inhibitors result in better visual acuity than in patients treated with laser photocoagulation or sham injection. The number of injections required for long-term improvement as well as the general long-term efficacy is unknown. The evidence is not sufficient to confirm the safety of the products in patients with DMO and does not suggest the superiority of a single product. They concluded that for some patients with DMO, VEGF inhibitors seem to be more effective as a short-term treatment option than alternative therapies. Decisions on financing should take into account the high price difference between the products and ongoing research.[2]

Jiang *et al*. compared the treatment patterns of anti-vascular endothelial growth factor and laser therapy among patients with diabetic macular edema. A diabetic macular edema is a form of diabetic retinopathy caused by continued leakage from retinal blood vessels. The use of anti-vascular endothelial growth factor injections has gained in popularity in the treatment of DME due to satisfactory efficacy, while laser photocoagulation is still the first-line therapy. Examining anti-VEGF treatment patterns may improve understanding of real-world medication-taking behaviors retrospective cohort analysis was conducted with Texas Medicaid medical and prescription claims for patients who were aged 18–63 years, continuously enrolled 1-year pre- and post-index, diagnosed with DME, and treated with anti-VEGF or laser therapies. Treatment patterns included treatment frequency and switching between anti-VEGF and laser therapies. Logistic regression and multinomial analysis were used to determine factors associated with switching and initiation of anti-VEGF therapy while controlling for demographic and clinical characteristics. Patients who switched from anti-VEGF injections to laser surgery were more likely to be Hispanic males who have fewer prescriptions and less likely to have no visual impairment. Multinomial regression results showed that anti-VEGF users were more likely to remain on the same therapy if they had more prescriptions. They concluded that anti-VEGF use is increasing; laser use is still more prevalent. Over 40% of patients who initiated anti-VEGF injections switched to laser surgery. Additional research should be conducted to determine factors associated with this high rate of switching.[5]

Studies also proved that the anti-VEGF factors inhibit vascular endothelial growth factors.[6-12]

This is not only used in the treatment of diabetic macular edema but used in series of conditions such as macular edema secondary to central retinal vein occlusion and branch retinal vein occlusion.[13,14]

The anti-VEGF treatment has also been proved to be effective for long term.[12]

We see an improvement in vision and a decrease in macular thickness post-anti-VEGF therapy. Figure 5 shows that the difference in macular thickness between pre- and post-anti-VEGF therapy increases with an increase in the initial macular thickness.

CONCLUSION

The current study shows that there is an improvement in the vision with anti-VEGF treatment. We also found that there is a decrease in macular thickness with treatment. It has been noted that higher macular edema more efficient the anti-VEGF therapy is. Hence, we can conclude that the anti-VEGF therapy is efficient in the treatment of diabetic retinopathy.

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Original Article

Study of Clinical Profile of Stroke in a Tertiary Care Centre – A Retrospective Study

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Abstract

Introduction: Cerebrovascular accident (CVA) is a global health problem and the leading cause of mortality and morbidity worldwide. Stroke is the second leading cause of death and the third leading cause of disability across the world. Each year, nearly 6 million people worldwide die from stroke.

Aim: This study aimed to analyze the clinical profile of CVA patients.

Materials and Methods: This prospective observational study was carried out in 30 consecutive patients with CVA. After taking consent, patients were subjected to clinical and laboratory investigation and the results were analyzed statistically and discussed below.

Results: Out of 30 patients, 20 were males, and 10 were females. About 56.7% of patients were above 61 years, followed by 33.3% in 51–60 years. Hypertension and diabetes mellitus are the most common risk factors in the patients. Twenty-two patients had an ischemic stroke, and eight patients had a hemorrhagic stroke.

Conclusion: Developing countries like India are facing a double burden of communicable and non-communicable diseases. Stroke is one of the leading causes of death and disability in India.

Key words: Cerebrovascular accident, Hemorrhagic, Ischemic, Stroke

INTRODUCTION

Stroke is the second leading cause of death and the third leading cause of disability across the world.[1,2] The incidence and prevalence of stroke vary depending on the demographics and habits, and the outcome is dependent on the treatment at their disposal. Stroke, also called a "brain attack" because it involves an acute insult to the brain, is a major disabling disease.[3] Among all neurological diseases of older life, cerebrovascular events rank the first in frequency and importance. Stroke after heart disease and before cancer is the most common cause of death.[4]

In India, community surveys have shown that hemiplegia's crude prevalence rate is in the range of 200/1,00,000 persons, nearly 1.5% of all urban hospital admissions, and 4.5% of all medical and around 20% of Neurologic cases.[5] Atherosclerosis is the most common cause of cerebrovascular stroke. It leads to stroke either by situ stenosis or occlusion or embolizing plaque material to distal cerebral vessels. The mortality rate of stroke in the acute phase is as high as 20%. It remains higher for several years after the acute event in the stroke population than in the general population.[6]

Cerebrovascular diseases include ischemic stroke, hemorrhagic stroke, and cerebrovascular anomalies such as intracranial aneurysms and arteriovenous malformations. Stroke is becoming an important cause of premature death and disability in low-income and middle-income countries like India, largely driven by demographic changes and enhanced by the increasing prevalence of the key modifiable risk factors. Risk factors for cerebrovascular accident (CVA) are divided into modifiable and non-modifiable risk factors. Non-modifiable risk factors include age, sex, ethnicity and geography, and family history of stroke.[7,8] Modifiable risk factors are smoking, alcohol consumption, drug abuse, arterial hypertension

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(HTN), diabetes mellitus (DM), dyslipidemia, and heart disease.[7,9,10]

The poor are increasingly affected by stroke because of both the changing population exposures to risk factors and, most tragically, not being able to afford the high cost of stroke care. The majority of stroke survivors continue to live with disabilities. The costs of on-going rehabilitation and long-term-care are largely undertaken by family members, which impoverish their families.[11] Effective risk factor intervention offers real hope of reducing stroke mortality and morbidity. Due to the increase in the burden of stroke in the coming years and the limited availability of stroke care in India, it would be better to study preventive measures that will help red stroke incidence.[12]

Aim

This study aimed to analyze the clinical profile of CVA patients.

MATERIALS AND METHODS

This prospective observational study was carried out in 30 consecutive patients with CVA. After taking consent, patients were subjected to detailed clinical history, clinical examination, and investigations. Risk factors for CVA such as HTN, diabetes, dyslipidemia and family history of CVA were evaluated. Patients were subjected to a computed tomography (CT) scan of the brain and other relevant investigations about their clinical status. Special investigations suchas magnetic resonance imaging brain, CT angiography, and magnetic resonance angiography were done wherever necessary. The risk factor profile of each patient was evaluated during the hospital stay. Results were analyzed statistically and discussed below.

RESULTS

In this study, 30 patients with stroke have been included. Out of 30 patients, 20 were males, and 10 were females. About 56.7% of patients were in age group more than 61 years, followed by 33.3% in 51–60 years age group [Figures 1-3].

Comorbid and risk factors, 17 patients had DM, 18 patients had HTN, two patients had smoking, and six patients had alcohol.

Fifteen patients had hemiplegia, nine patients had slurring speech, three patients had UMN facial palsy, four patients had altered sensorium, one had convulsions, five patients had a headache, nine patients had vomiting, five patients had giddiness, and 12 patients had the inability to gait [Figure 4].

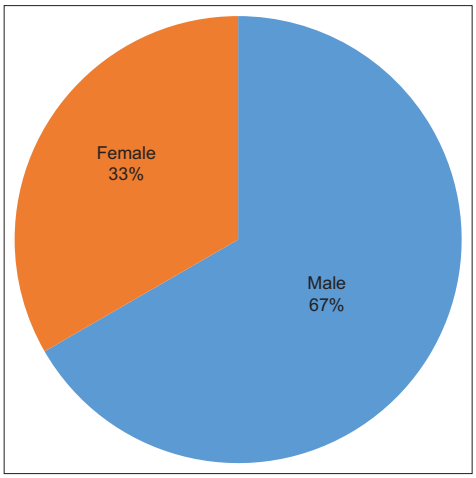

Figure 1: Gender distribution

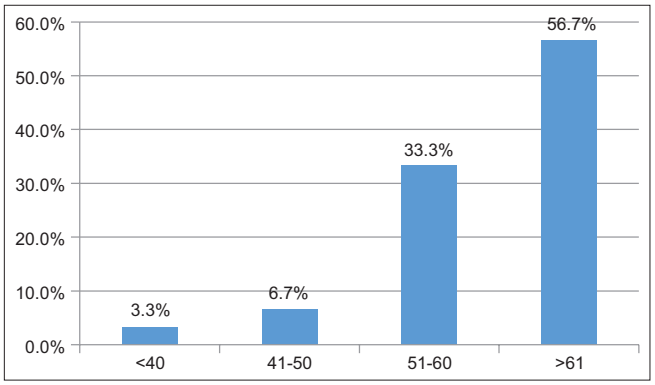

Figure 2: Age distribution

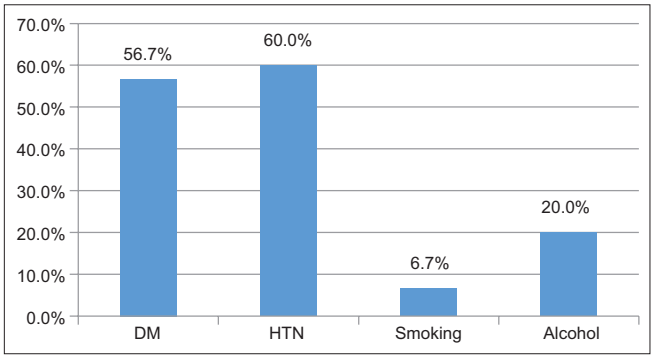

Figure 3: Risk factors

The stroke type, 22 patients had an ischemic stroke, and eight patients had a hemorrhagic stroke [Figure 5].The topographic of stroke, one patient had an intraparenchymal hemorrhage, two patients had intracerebral hemorrhage (ICH), one had an intraparenchymal and intraventricular hemorrhage, two patients had thalamic infarct, and two patients had a subarachnoid hemorrhage [Table 1].

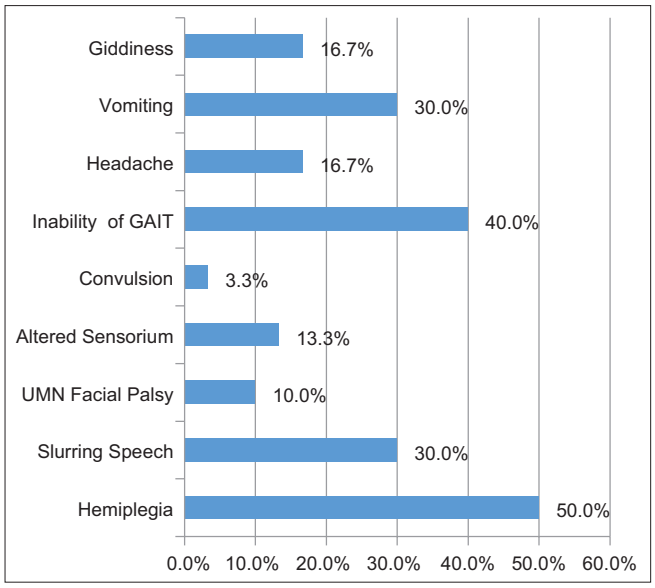

Figure 4: Clinical presentation

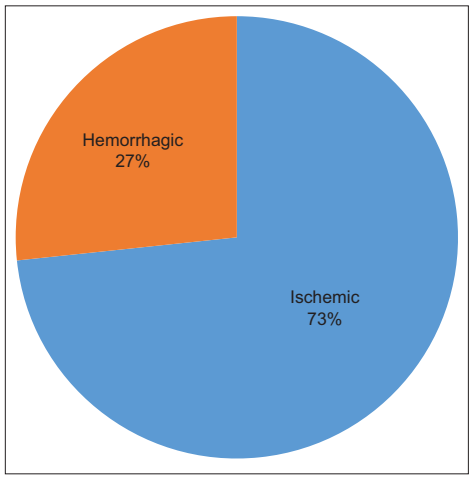

Figure 5: Types of stroke

Table 1: Topographic of stroke

Topographic of stroke	Hemorrhagic	Ischemic
Intraparenchymal Hemorrhage	1	0
ICH	2	1
Intraparenchymal and intraventricular hemorrhage	1	0
Ischemic stroke	0	3
Thalamic infarct	2	3
Non-hemorrhagic infarct	0	1
MCA infarct	0	12
Pontine infarct	0	2
Subarachnoid hemorrhage	2	0

ICH: Intracerebral hemorrhage, MCA: Middle cerebral artery

DISCUSSION

CVA caused 5.7 million deaths in 2005, and 87% of deaths are reported in low- and middle-income countries.[13] It is the second most common cause of death worldwide.[14] Developing countries account for 85% of global deaths due to stroke, and 15%–30% of stroke patients are permanently disabled.[15] In India, a community survey has shown a crude prevalence rate for hemiplegia in the range of 200/100000 persons, nearly 1.5% of all the urban hospital admission, 4.5% of all medical, and around 20% of all neurological cases.[16] In India, the prevalence of stroke various in different regions of the country, and the estimated prevalence is 12–20/1000 in the 75–84 years' age group.[12]

In our present study, most study population were in the age group of above 60 years, which is similar to the study done by Jain *et al.* study[17] and Bhadada *et al.* study,[18] Sharma *et al.*,[19] and Idicula *et al.*[20]

In this study, male predominance was present, and similar findings were observed in Anand *et al.*, Nagaraj *et al.*, and Marwat *et al.*; study.[21-23]

In this study, HTN was the most common risk factor, and similar findings were observed in Marwat *et al.*; and Pandiyan *et al.* study.[21,24] In this study, 17 patients (39%) had DM, which correlates with Sorganvi *et al.*; study.[12]

In our study, subarachnoid hemorrhage was more common. However, studies done by Vaidya and Majmudar and Patne and Chintale reported the most common site of infarction as various lobes of cerebral hemispheres.[25,26]

Hemiplegia was the most common presenting feature, followed by gait inability in the present study, similar to the other studies were hemiplegia which was the most common presenting feature.[25,26]

CONCLUSION

India, like other developing countries, is in the midst of a stroke epidemic. There is a huge burden of stroke with significant regional variations of stroke in our county. Public awareness of the risk factors and their management may lead to the primary prevention of CVA. Early hospitalization of patients and their management reduces the mortality and disability in CVA.

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Original Article

Study of Clinical Profile of Acute Myocardial Infarction in Tertiary Care Center: A Retrospective Study

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Abstract

Introduction: Coronary artery disease (CAD) is one of the most common causes of mortality and morbidity in developed and developing countries. The prevalence of classic cardiovascular risk factors such as hypertension, dyslipidemia, obesity, and diabetes varies widely between different countries and shows some important secular trends.

Aim: This study aims to study the clinical profile and risk factor of CADs.

Materials and Methods: A total of 42 patients with a confirmed diagnosis of CADs were included in this study. Patient demographic, presentation, and examination data were collected analyzed. Results were analyzed using appropriate statistical tools.

Results: Out of 42 patients, 31 were male, and 11 were female; 78.6% were more than 51 years age group. Hypertension, diabetes, and both were more common comorbid in the patients. Chest pain was the most common symptoms, 71.4% were had ST-elevation myocardial infarction (MI) and the majority had single-vessel CADs. About 64.3% of patients underwent percutaneous transluminal coronary angioplasty.

Conclusion: Early identification of risk factors is vital to avoid the incidence of coronary heart disease, as is community knowledge of risk factors, symptoms, and signs of acute MI so that early referral to a coronary care unit may be made to minimize morbidity and mortality in the community.

Key words: Coronary artery diseases, Diabetes, Electrocardiogram, Hypertension, Risk factors

INTRODUCTION

Coronary artery disease (CAD) is one of the most common causes of mortality and morbidity in developed and developing countries. The prevalence of classic cardiovascular risk factors such as hypertension, dyslipidemia, obesity, and diabetes varies widely between different countries and shows some important secular trends. The second half of the 20th century has witnessed a global spread of the CAD epidemic, especially in developing countries, including India. The WHO predicts the global burden of cardiovascular disease (CVD) with increasing mortality and economic burden on health care.[1]

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CAD is a type of blood vessel disorder included in the general category of arteriosclerosis. Arteriosclerosis is often referred to as "hardening of the arteries" and begins as soft deposits of fat that hardens with age.[2-4] Atheroma's has a preference for the coronary arteries. CAD occurs when the arteries that supply blood to the heart muscle (coronary arteries) become hardened and narrowed. The arteries harden and become narrow due to the buildup of plaque on the arteries' inner walls or lining (atherosclerosis). Blood flow to the heart is reduced as plaque narrows the coronary arteries. This decreases the oxygen supply to the heart muscle. Atherosclerotic heart disease, cardiovascular heart disease, ischemic heart disease, coronary heart disease, and CAD are synonymous terms used to describe this disease process.[2]

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India has one of the highest burdens of CVD worldwide. The annual number of deaths from CVD in India is projected to rise from 2.26 million (1990) to 4.77 million (2020).[5] Coronary heart disease prevalence rates in India have been estimated over the past several decades and have ranged from 1.6% to 7.4% in rural populations and from 1% to 13.2% in urban populations.[6] The INTERHEART study showed that CVD risk factors such as abdominal obesity, hypertension, and diabetes are higher among Indians, even at young ages than among other ethnic groups.[7] The prevalence rates of CVD risk factors have been rapidly rising within India over the past 25 years, particularly within urban communities.[8]

Aim

This study aims to study the clinical profile and risk factor of CADs.

MATERIALS AND METHODS

This retrospective study was conducted to analyze the clinical profile and risk factor of CADs. A total of 42 patients with a confirmed diagnosis of CADs were included in this study. All the particulars were inquired by a questionnaire containing their history, personal h/o, and family h/o. All the patient's demographic details were collected, thorough clinical history and clinical examination, routine laboratory investigation had done. Blood samples were collected for blood glucose and serum lipid profile estimation, and resting electrocardiogram (ECG) was recorded. Patients were managed as per hospital protocol. Results were analyzed using appropriate statistical tools.

RESULTS

Out of 42 patients, 31 were male, and 11 were female [Table 1].

Out of 42 patients, 31 were male, and 11 were female. Based on age group, 2 were below 40 years, 7 were between 41 and 50 years, 10 were between 51 and 60 years, and 23 patients had more than 60 years [Table 2].

Out of 42 patients, 31 were male, and 11 were female. Based on the risk factor, 17 patients had hypertension, 2 patients had diabetes, 14 patients had hypertension and diabetes, 12 patients had a habit of smoking, 9 patients had a habit of alcohol conception, and 6 patients had hypercholesterolemia [Table 3].

Based on symptoms, 41 patients had chest pain, 14 patients had perspiration, 11 patients had palpitation, 3 patients had syncope, 7 patients had nausea and vomiting, and 9 patients had dyspnea [Table 4].

Thirty-one patients had single-vessel diseases, seven patients had double-vessel diseases, and four patients had triple-vessel diseases [Table 5].

Based on ECG, 30 patients had ST-elevation myocardial infarction (STEMI), 7 patients had non-STEMI, and 5 patients had ischemia [Table 6].

Based on treatment, 14 patients had thrombolyzed, 27 patients had percutaneous transluminal coronary angioplasty, and 1 patient had coronary artery bypass grafting (CABG) [Table 7].

DISCUSSION

In this present study, most were male than females; most of the affected were older age populations. Hypertension and diabetes are the major risk factor among the study population. Chest pain was the common symptoms followed by perspiration, and the majority of the population ECG changes shows STEMI. Three-fourth study population had single-vessel diseases.

Zuhdi *et al.*[9] categorized the patients into young (<45 years for men and <55 years for women) and old (45 years and older for men and 55 years and older for women). There were 1595 patients, of which 16% were categorized into the young CAD group and were significantly associated with more active smoking and obesity than the older group. The study also found a preponderance toward single-vessel disease in the young CAD group with better clinical outcomes.

CAD generally affects men more than women. Lee *et al.*[10] studied the various aspects of gender differences in 10,554 PCI patients. Women, on average, were 5 years older than men at presentation and with a higher prevalence of risk factors. The in-hospital and 6-month mortality were also higher in women. In another paper, Lu *et al.*[11] looked into the differences in gender and found that among 13,591 patients, 24.2% were women. They had more risk factors, were unlikely to undergo intervention, and had higher mortality.

Idris *et al.*[12] studied explicitly on the woman of reproductive age. The authors reported that out of 9702 patients, 24.2% were female. Still, only 1.9% were at the reproductive period (from 20 to <40 years of age) and were associated with an Indian ethnicity, diabetes mellitus, and hypertension. Young female patients commonly present with STEMI and have a poorer prognosis.

Murty *et al.*[13] reviewed 5579 autopsy reports done at University Malaya Medical Centre from 1996 to 2005 to study the prevalence of cardiac deaths in females and

Table 1: Gender distribution

Gender	Frequency	Percentage
Male	31	73.8
Female	11	26.2

Table 2: Age distribution

Age group	Frequency	Percentage
<40	2	4.8
41–50	7	16.7
51–60	10	23.8
>61	23	54.8

Table 3: Risk factors

Risk factors	Frequency	Percentage
HTN	17	40.5
DM	25	59.5
HTN+DM	14	33.3
Smoking	12	28.6
Alcohol	9	21.4
Hypercholesterolemia	6	14.3

HTN: Hypertension; DM: Diabetes mellitus

Table 4: Symptoms

Symptoms	Frequency	Percentage
Chest pain	41	97.6
Perspiration	14	33.3
Palpitation	11	26.2
Syncope	3	7.1
Nausea and vomiting	7	16.7
Dyspnea	9	21.4

Table 5: Type of CADs

Type of CAD	Frequency	Percentage
Single-vessel disease	31	73.8
Double-vessel disease	7	16.7
Triple-vessel disease	4	9.5

CADs: Coronary artery diseases

found that 83 out of 936 female deaths were due to cardiac causes. The three leading causes reported in the study were advanced CAD (14.5%), hypertensive heart disease (13.3%), and coronary atherosclerosis (12.0%). The study said that hypertension, diabetes, and pre-menopausal age were the most significantly associated factors.

Chiam *et al.*[14] studied the prevalence of ethnicity and conventional risk factors of diabetes mellitus, hypertension, and hyperlipidemia in 302 patients admitted for CABG in their center. Indian patients were associated with a combination of all three risk factors, while the Chinese and Malays mainly were associated with hypertension and hyperlipidemia.

Table 6: ECG changes

ECG	Frequency	Percentage
STEMI	30	71.4
NSTEMI	7	16.7
Ischemia	5	11.9

ECG: Electrocardiogram, STEMI: ST-elevation myocardial infarction, NSTEMI: Non-ST-elevation myocardial infarction

Table 7: Treatment modalities

Treatment	Frequency	Percentage
Thrombolyzed	14	33.3
PTCA	27	64.3
CABG	1	2.4

CABG: Coronary artery bypass grafting, PTCA: Percutaneous transluminal coronary angioplasty

Dhanjal *et al.*[15] compared the cardiovascular risk factors profile of Asian patients admitted with myocardial infarction (MI) in a hospital in Kuala Lumpur (42 patients) and Birmingham, U.K. (28 patients), with Caucasian patients admitted with MI in Birmingham (20 patients). The study found a higher prevalence of diabetes among Asians in both countries than Caucasians, which may explain the higher prevalence of CAD in this ethnic group regardless of locality.

Echocardiography, particularly stress echocardiography, is a valuable investigation in patients at intermediate or high risk of CAD. However, interpretation of the acquired images is subjective and depends on the acoustic windows. Acharya *et al.*[16] studied various grayscale features of echocardiography images from a database of 400 CAD cases and 400 normal and compiled all the features that had good discriminating capability into a Gaussian mixture model classifier.

Lee *et al.*[17] retrospectively reviewed 192 STEMI cases who received thrombolysis using streptokinase and found reperfusion failure rate using ECG criteria of 56.8% associated with diabetes mellitus, hypertension, anterior MI, longer door-to-needle time, and high total white cell.

CONCLUSION

This study concluded that older people were most probably, and hypertension and diabetes are the significant risk factors for CADs. Urgent steps are needed to modify lifestyle by increasing physical activity, changing diet, and perhaps making aggressive use of statins as part of the preventive strategy to reduce risk factors and, thus, the burden of CAD.

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