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Case Report

Hand Foot and Mouth Disease – A Case Report and Review of Literature

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Abstract

Hand, foot, and mouth disease (HFMD) is a quotidian viral illness affecting primarily infants and children but can sometimes affect adults too. As the name propounds, the infection usually involves the hands, feet, and mouth, although may, sometimes, involve the genitals and buttocks. The genesis of HFMD is coxsackievirus A type 16 in most cases, but other strains of coxsackieviruses and Enteroviruses can also be the culprits. The coxsackievirus is a member of the *Picornaviridae* family, which includes non-enveloped single-stranded RNA viruses. This article aims to review the pathophysiology and clinical presentation of HFMD by discussing a case and will aim to highlight the role of the dental clinicians in diagnosis and management of this disease entity.

Key words: Coxsackievirus, Enteroviruses, Hand, foot, and mouth disease, *Picornaviridae*

INTRODUCTION

Hand, foot, and mouth disease (HFMD) is a common disease encountered usually in childhood and is characterized by a brief febrile illness, archetypal vesicular rashes on the palms, soles, or buttocks, and oropharyngeal ulcers. Occasionally, patients may also develop neurological complications, such as encephalomyelitis, aseptic meningitis, and acute flaccid paralysis. The most common etiological culprits are coxsackievirus A6, A16, and *Enterovirus* type 71.[1,2] Here, we report and discuss a case in a year male child who presented with typical features of HFMD.

CASE REPORT

A 4-year-old male patient reported to the outpatient department with chief complaints of difficulty in eating since a day and history of fever since 2 days. The patient was apparently alright 2 days back, when he suddenly developed a fever overnight. There were no prodromal symptoms of flu as such and the fever was of high grade associated with malaise and lethargy in general. The child was administered with plain paracetamol for his fever which eventually subsided. The following day, his mother noticed multiple papules over the palm and foot. Following that he rapidly developed a severe ache in both legs and was unable to eat. The eruptions were associated with severe itching over the papules.

After obtaining a proper informed consent from the parent as part of the routine protocol before the clinical examination, the patient was carefully examined. The child on inspection looked sluggish and overall lethargic and irritable. On palpation, the patient was febrile and a digital thermometer was used to check the temperature which was high at 101.4°F at the time of presentation. Multiple papules were noted on the palm [Figure 1] and foot [Figure 2]. On intraoral examination, multiple reddish macules, measuring approximately 2 mm in diameter, were apparent in the roof of the hard palate (in rugae area and along the junction of hard and soft palate) [Figure 3]. No other lesions were present intraorally. Based on the clinical presentation, the case was diagnosed as hand, foot and mouth disease. The patient's parent was advised to give him plenty of fluids, along with a prescription of paracetamol syrup for fever besides topical local

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Figure 1: Photograph showing numerous papules on palm

Figure 2: Photograph showing numerous papules on foot

Figure 3: Photograph showing numerous macules scattered over hard palate

anesthetic for intraoral application, antihistamine syrup to reduce itching, and calamine lotion for topical application on the lesions. The parents were asked to come for follow-up after 2 days. After 2 days, most of the papules had turned into fluid-filled blisters and few blisters were present around the mouth. The palatal lesions had considerably subsided, thus improving the patient's ability to consume food. The vesicles showed crustations in a week's time and the skin eventually returned to normal in a month. The patient was followed up for 6 months without any recurrence till date.

DISCUSSION

First reported in New Zealand in 1957, HFMD is a routinely confronted, for the most part a mild, childhood illness caused by Enteroviruses. It is a viral exanthem, and it is most commonly caused by the coxsackievirus of the *Enterovirus* family. Coxsackievirus A16 and *Enterovirus* A71 are the serotypes most commonly implicated as causative agents.[3-5] The past 5 years, coxsackievirus A6 has been identified as a causative agent in outbreaks in Europe, South-East Asia, and America.[6] Coxsackievirus A16 was first identified in 1958 in Canada. HFMD has been considered to be a benign disease of self-limiting nature.[7] Although not indigenous to one area in particular, it occurs worldwide. As children (particularly those younger than 7 years of age) are more vulnerable, they tend to be infected at a higher rate than adults. Ergo, outbreaks are more frequently seen in day-cares, summer camps, or within the family. Inputs from Large-scale surveillance in China have clearly demonstrated that more than 90% of HFMD cases occurred in children <5 years of age with a mortality of around 0.03%. It was also concluded that cases tended to occur more frequently during late spring and early summer.[8] Another study from Vietnam reported a positive interdependency between an increase in environmental temperature and humidity and an increase in the incidence of HFMD.[9]

In 2021, a French surveillance found a meteoric increase in HFMD cases, with more than 3400 cases being officially reported. More than 90% of sequenced cases were found to be linked to *Enterovirus,* while few atypical cases were found to be associated with Coxsackievirus A6 and A16.[10] In United States, Coxsackievirus A6 remains the dominant cause of HFMD[11] till date.

The spread of the human *Enterovirus* is conciliated by oral ingestion of the shed virus from the gastrointestinal or upper respiratory tract of infected hosts or through vesicle fluid or oral secretions.[12] The patients tend to be most infectious in the 1st week of the disease, with an incubation period ranging between 3 and 6 days.[12] Post ingestion, the virus replicates primarily in the lymphoid tissue of the lower intestine and the pharynx and fan out to the regional lymph nodes. This can later extend to multiple organs, including the central nervous system (CNS), heart, liver, and skin.

HFMD can initiate with a low-grade fever, loss or reduced appetite, and general malaise. The quintessential presenting symptom is usually mouth or throat pain secondary to the exanthem which can be macular, papular, or vesicular. The lesions are about 2–6 mm in size, are non-pruritic, and are typically not painful. They last on an average of 10 days, tend to rupture, and result in painless and shallow ulcers that do not leave a scar. The dorsum of the hand, feet, buttocks, legs, and arms can also be involved. The vesicles are surrounded by a thin halo of erythema, eventually rupturing and forming superficial ulcers with a gray-yellow base and an erythematous rim. Oral lesions commonly involve buccal and tongue ulcers but may also strike the soft palate.[12]

On rare occasions, HFMD has presented with atypical features like concomitant aseptic meningitis. *Enterovirus* infections that cause HFMD are notorious for involving the CNS and may cause encephalitis, polio-like syndrome, acute transverse myelitis, Guillain-Barre syndrome, benign intracranial hypertension, and acute cerebellar ataxia.[12]

The diagnosis of HFMD is usually made clinically. The virus can be detected in the stool for about 6 weeks after infection; however, shedding from the oropharynx is generally <4 weeks. Light microscopy of biopsies or scrapings of vesicles will differentiate HFMD from varicella-zoster virus and herpes simplex virus. While serology is not sensitive to making a diagnosis of HFMD, levels of IgG can be used to monitor recovery. Some centers use serological methods are to differentiate *Enterovirus* 71 from coxsackievirus, due to its prognostic magnitude. Latterly, polymerase chain reaction assays are also available in many centers to confirm the diagnosis of coxsackievirus. A swab of the lesion can detect coxsackievirus or *Enterovirus* using real-time PCR assays.[11,13]

HFMD is a relatively mild clinical syndrome and usually resolves within 7–10 days. The treatment is fundamentally symptomatic and supportive. Pain and fever can be easily managed with NSAIDs and acetaminophen. Making sure the patient remains well-hydrated is of paramount importance. In addition, a mixture of liquid ibuprofen and liquid diphenhydramine can be used to gargle, which helps coat the ulcers, easing the pain.[14,15] Steroids are useless as they were found to increase the risk of severe HFMD.[16]

In recent times, researchers have developed specific treatments to manage *Enterovirus* induced HFMD due to its severe neurological complications. Hitherto, no drug has been approved, but promising novel agents include molecular decoys, translation inhibitors, receptor antagonists, and replication inhibitors. An antiviral agent that has shown promising results in the treatment of *Enterovirus* is pleconaril, an anti-picornaviral agent. However, currently, there are no approved antivirals for the treatment of HFMD.[17] Anecdotal reports have shown some clinical response to acyclovir, but large-scale trials have not established this.[18]

Numerous vaccines have been developed against HFMD and enteroviruses. Lately, strain-specific inactivated whole-virus aluminium-adjuvant vaccines have been evolved in China and are approved for widespread use.[8] In a study with 10,077 participants, a three-dose regimen of the EV71 C4a vaccine showed an overall efficacy of 94.7% (95% CI 87.8–97.6), with protection lasting for around 2 years.[19] Virus-like particles vaccines, DNA vaccines, peptide vaccines, and subunit vaccines have been developed but are in various stages of clinical trials.[20]

CONCLUSION

It is not new information that there is a remarkable link between one's oral health and overall health. Ergo, it is paramount the, dental surgeons must be aware of the correlations, assess patients for risk factors, and encourage patients to follow-up with their physician for age-appropriate screenings. Numerous systemic conditions, including some autoimmune, hematologic, endocrine, and neoplastic diseases as well as chronic illnesses, cause pathognomonic changes in the oral cavity. Dental practitioners play a key role in preventive medicine as they work with their medical cohorts to identify systemic diseases. Together, the medical and dental homes are integral to a superior and an acceptable patient health.

HFMD, that was once considered a disease of cattle, has been emerging as a common human childhood disease in the past few years. Although in most of the cases, it is nonfatal, there are some reported cases of complications seen in HFMD patients. Therefore, all dentists, pediatricians, and dermatologists should be aware of the clinical features of this disease and its possible complications so that it can be dealt with caution.

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Case Report

Maculopapular Cutaneous Mastocytosis Presentation with Elevated Serum Tryptase Levels (>20 μg/L): A Case Report

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Abstract

Cutaneous mastocytosis is a rare group of diseases characterised by the abnormal accumulation and proliferation of mast cells in the skin. There are three recognized forms: Diffuse cutaneous mastocytosis, cutaneous mastocytoma and, the most common form, maculopapular cutaneous mastocytosis. Pediatric patients are relatively rare to suffer from cutaneous mastocytosis. The presented case of 9-month-old male infant with respiratory distress and coughing for 2 days, along with dark raised and flat lesions all over his body for 4 months. Skin biopsy showed uniformly spindle-shaped cohesive aggregates of mast cells filling the papillary and mid dermis. A modest increase in perivascular mast cells was identified. Toluidine blue wet stains of the tissue showed a striking cluster of mast cells in the dermis observed in purple to red color. Even though serum tryptase >20 μg/L, there is no evidence of marrow involvement. A retrospective review of literature on pediatric cutaneous mastocytosis in Indian scenarios demonstrated that serum tryptase levels are significantly higher.

Key words: Bone marrow, Cutaneous mastocytosis, Tryptase

INTRODUCTION

Mastocytosis is a disorder of mast cells characterized by multifocal compact clusters or cohesive aggregates. The disorder is heterogeneous with skin or multi-organ involvement (cutaneous/systemic involvement). In cutaneous mastocytosis, atypical/normal mast cells accumulate in the dermis due to increased proliferation and decreased apoptosis. A recent WHO classification recognizes them as diffuse cutaneous mastocytosis, cutaneous mastocytoma, and maculopapular cutaneous mastocytosis, the most common form.

CASE REPORT

A 9-month-old male infant is brought with a complaint of respiratory distress, fever, and cough for 2 days. Complain of dark to red colored raised and flat lesions associated with itching all over the body for 4 months. Lesions started initially over the face and neck and slowly progressed to involve the trunk over 2 months. Lesions are erythematous and later hyperpigmented and associated with itching. Past history of chicken pox, no relevant other histories (vomiting/food allergy/abdominal pain/diarrhoea/family history). On physical examination Figure1 illustrates, multiple erythematous to hyperpigmented macules and plaques are present on the face, trunk, scalp, and neck. No involvement of hair, nails, oral, and genital mucosa. Darier's sign is positive.

Laboratory workup showed elevated serum tryptase level (27.9 μg/L, Method: floroenzyme immunoassay), and peripheral blood smear reveals mild eosinophilia (1.22 × 10^3 micro/L) with thrombocytosis. Ultrasonography works up to finding negative for organomegaly. Subsequently, a skin biopsy was performed.

Histopathological studies as illustrated in Figure 2 showed epidermal spongiosis with basal layer hyperpigmentation. Uniformly spindle-shaped cohesive aggregates of mast cells fill the papillary and mid dermis. A modest increase in perivascular atypical mast cells was identified. Toluidine

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Table 1: Comparisons of MPCM studies with elevated tryptase level

Study	Carter *et al*.[16] (>20 μg/L)	Schwartz *et al*.[11] (>20 μg/L)	Sathishkumar *et al*.[17] (>24 μg/L)
MPCM cases count	12.5%	23%	30.7%

blue wet stains of the tissue showed a striking cluster of mast cells at the dermis in purple to red in color. In view of raised tryptase levels (>20 μg/L) to rule out systemic mastocytosis, bone marrow studies were performed. Diluted aspirates show an increase in eosinophilic precursors and mast cells. Mastocytosis can present with hypogranular mast cells (atypical) which are appreciated by CD117, but aspirated smears are negative for mast cell clusters. Based on the above evidence, cutaneous mastocytosis is rendered and the toddler was kept under follow-up.

DISCUSSION

Cutaneous mastocytosis is identified by the clinical presentation of skin lesion associated with Darier's sign in addition to the absence of systemic mastocytosis. Histological presence of increased mast cells (in clusters) in the dermis by 4–8-fold in the lesion compared to the skin of healthy subjects or increase of mast cells by 2–3-fold compared with those in the skin of patients with inflammatory cutaneous disease.[1-7]

Maculopapular cutaneous mastocytosis (urticaria pigmentosa) is the most common manifestation of mastocytosis among children. MCPM is classified into monomorphic and polymorphous lesions clinically. Often, children with polymorphous MPCM exhibit brown or red lesions of different sizes with sharp or indistinct margins, as well as flat or elevated lesions. Over time, lesions commonly spread to the upper trunk, distal extremities, and lateral neck, starting on the thigh, axilla, or lower trunk. The skin on the face is usually spared.[8,9] There is a wide range of lesions among patients, ranging from fewer than 10 lesions to almost universal coverage, and the number may correlate with systemic involvement, as well as with serum tryptase.[10]

Most of the cutaneous mastocytosis had (B12) tryptase levels <20 μg/L, while systemic disease patients had levels above 20 μg/L.[11] The presence of MPCM with serum tryptase levels above 20 μg/L raises suspicions of systemic mastocytosis, subsequently leading to bone marrow testing, which is more likely to yield negative results. Routine Peripheral blood smears in mastocytosis are often normal with minority of cases show evidence of abnormal proliferation of cells of one or more myeloid lineage (neutrophils, eosinophils, basophils, monocytes, or thrombocytosis).[12,13] cutaneous mastocytosis in pediatric population has hypocellular smear with increased

Figure 1: Clinical presentation of maculopapular cutaneous mastocytosis on inspection. (a) Inspection of the child on ventral and dorsal (b) Aspect shows hyperpigmented macules and plaques Involving face, trunk, scalp and neck

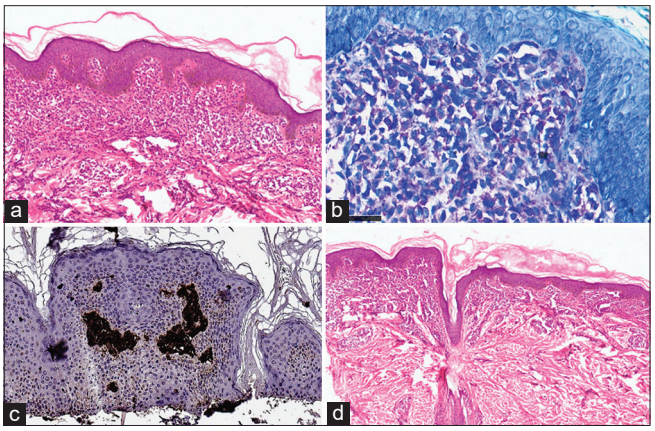

Figure 2: Microscopy of Maculopapular cutaneous mastocytosis. (a and d) (scale 200 μm) showing uniformly spindle-shaped cohesive aggregate of mast cells filled the papillary area and the mid dermis. (b) (scale 200 μm) Tolidine blue staining of skin highlights mast cells in purple colour. (c) (scale 50 μm) section from skin showing CD117 IHC highlighting mast cells in epidermis in a exhausted skin block of cutaneous

hematogones in bone marrow aspirate smears.[14] There may be mild erythroid and megakaryocytic dysplasia. Bone marrow biopsy shows focal perivascular and peritrabecular location of mast cells, eosinophils, and early myeloid cells.[15] Comparing with various studies as showed in the Table1 above, Southern Indian population are tend to have higher serum tryptase levels.

MPCM is less likely associated with bone marrow involvement or organomegaly, but if present, they are usually associated more with hepatomegaly. In follow-

up bone marrow studies in MPCM, its observed that biopsies are normocellular to hypocellular with 27% of cases showing increased mast cells (typical) in addition 9% of cases demonstrated mast cell aggregates (<15 cell). All the cases were resolved or partially resolved with no transformation into systemic mastocytosis in follow-up biopsy after 20-years.[18]

CONCLUSION

It has been observed that few pediatric MPCM cases with relatively higher or marginally elevated serum tryptase levels (>20 μg/L) at initial presentation are less likely to have underline systemic disease (especially in the South Indian population). The threshold point of suspecting underlining systemic disease by serum tryptase level is relatively higher in the South Indian population. Perhaps it's better to keep such cases under annual follow-up check-ups and teleconsultations once every 6 months rather than recommended for bone marrow studies to rule out systemic mastocytosis, especially at the initial encounter.

More analytical studies should be done to judge the threshold point on serum tryptase levels to know when should we suspect underlining systemic mastocytosis in the Southern Indian pediatric population.

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Case Report

Pleomorphic Adenoma Involving the Palate – A Case Report and Brief Review

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Abstract

Pleomorphic adenoma (PA) is the most commonly encountered benign salivary gland neoplasm which generally affects major and less frequently minor salivary glands. The commonest intraoral site is the palatal area. Minor salivary gland tumors have a higher risk of malignancy compared to tumors of the major salivary glands, so definite diagnostic evaluation is extremely crucial. Here, we present a histopathologically diagnosed and immunohistochemically confirmed case of PA of palate in a middle-aged female patient who presented with a palatal swelling present over a prolonged period of time (18 years).

Key words: Hard palate, Minor salivary gland, Mixed salivary gland tumor, Palatal tumor, Pleomorphic adenoma

INTRODUCTION

Salivary gland tumors constitute about 3% of the head and neck tumors.[1] In this context, pleomorphic adenoma (PA) is the most commonly encountered lesion, comprising approximately 60% of all salivary gland tumors.[2]

PA is associated with parotid gland in 53–77% cases, submandibular gland in 44–68%, and minor salivary glands in 4–6% of the cases.[3]

About 70% of the minor salivary gland tumors are PAs, while most commonly affected site in the oral cavity is palatal area, followed by lip, buccal mucosa, floor of mouth, tongue, tonsil, pharynx, and retromolar trigone.[4] PA of the hard palate presents as a painless, firm, and submucosal mass without ulceration or surrounding inflammation. Usually, they lack a well-defined capsule and frequently involve periosteum or bone.[5]

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This is a tumor of diverse histological and topographical presentation, with the essential components being the capsule, epithelial and myoepithelial cells, and the mesenchymal or stromal elements.[6]

Wide local excision with removal of the periosteum and involved bone is by far the treatment of choice. The potential risk of the PA to become malignant is about 6%.[7]

However, minor salivary gland tumors have a higher risk of malignancy compared to tumors of the major salivary glands, so definite diagnostic evaluation should be executed.[8]

This case report presents a case of histopathologically diagnosed PA of the palate in a middle-aged female patient and emphasizes on the need for awareness of its diverse presentation by the examining clinician that could significantly influence the treatment approach and prognosis.

CASE REPORT

A 54-year-old female patient reported to the department of oral and maxillofacial pathology with the chief complaint of a painless growth on the right side of palate.

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History revealed that the mass developed involving the right side of palate about 18 years ago, which was initially small and non-tender. It progressively enlarged to attain the present size, being associated with discomfort during mastication. There were no other symptoms (e.g., numbness, dysphagia, stridor, and speech difficulties) associated with the lesion. There was no history of trauma, fever, or similar swelling elsewhere in the body. Medical history revealed that the patient was healthy and had neither any systemic disease nor any deleterious habit.

The patient was moderately built and conscious, with a normal gait. Her vital signs were within normal limits. The extraoral examination showed no facial asymmetry or lymphadenopathy.

On intraoral examination, we noted the presence of a well delineated, sessile, dome-shaped swelling measuring approximately 4 cm × 3 cm involving right side of the palate, extending mediolaterally from the mid-palatine raphe to the area adjacent to 13–16, and anteroposteriorly from the area adjacent to 12 to that of 16. The overlying mucosa was smooth, stretched, non-ulcerated, and pale pink in color [Figure 1]. On palpation, the swelling was non tender, non-reducible, non-compressible, and non-pulsatile but slightly fluctuant in nature. It was soft to firm in consistency. No tendency of bleeding was present.

The orthopantomogram revealed thinning of antral and nasal floor. Cone-beam computed tomography (CBCT) revealed a round to oval radiolucency with corticated periphery and hypodense internal structure, having radiodensity similar to that of soft tissue or fluid [Figure 2]. The patient's routine hemogram was within normal limits.

Incisional biopsy was performed from the representative site, soft-tissue specimen was processed, and finally, the sections were stained with hematoxylin and eosin. The routine light microscopic histopathological evaluation revealed the presence of parakeratinized hyperplastic stratified squamous surface epithelium with underlying connective tissue. The deeper stroma was characterized by presence of neoplastic islands with diffuse spindle to polygonal cell differentiation, along with clear myoepithelial cells. Occasional foci of glandular differentiation with amorphous eosinophilic secretory deposits were noted. Fibrocollagenous changes and some areas of myxomatous changes were also present in the stroma [Figures 3 and 4]. The overall light microscopic features were suggestive of PA.

Then, the tissue block was sent for immunohistochemical analysis where the tumor was found to be immunopositive

Figure 1: Intraoral photograph showing a smooth surfaced sessile dome-shaped palatal mass

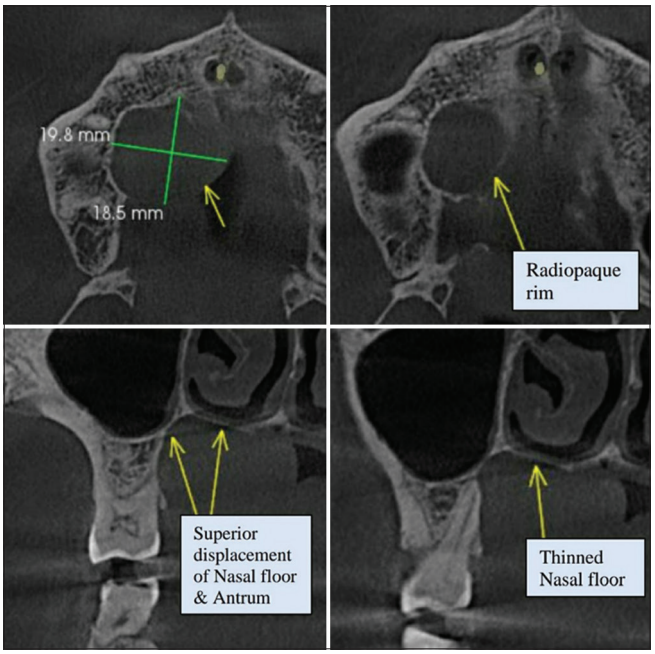

Figure 2: Cone-beam computed tomography showing ovoid radiolucency with corticated periphery and hypodense internal structure in the palatine area

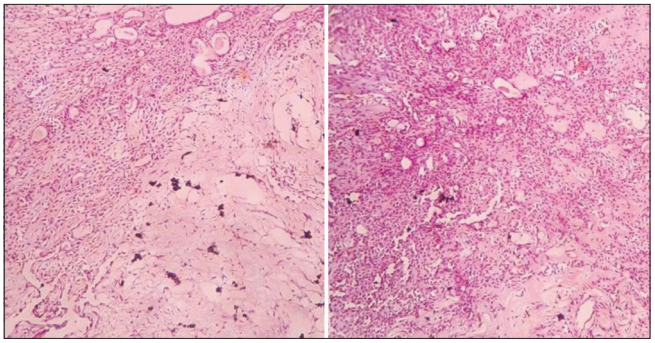

Figure 3: Photomicrograph showing hematoxylin and eosin stained sections in low power view (×10) revealing diffuse spindle cell and myoepithelial cell proliferation and myxomatous areas

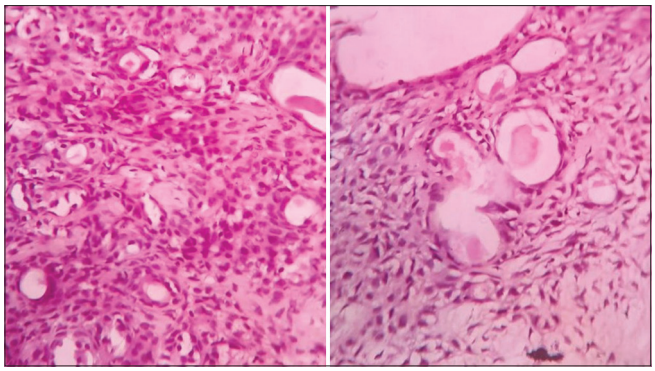

Figure 4: Photomicrograph showing hematoxylin and eosin stained sections in high power view (×40) revealing foci of glandular differentiation with eosinophilic secretory deposits

for Sox10/p63, CK19, CK14, SMA (focally). Hence, the diagnosis of the lesion was confirmed as PA of palate.

Then, the patient was sent to the department of oral and maxillofacial surgery where the mucoperiosteal flap was reflected, and the whole tumor mass was excised along with the mucoperiosteum while keeping the boundary line localized in the surrounding healthy tissue. A palatal plate was fabricated for the immediate post-operative period. The post-operative period was uneventful [Figure 5]. The patient is under regular follow-up, and there has been no evidence of recurrence after 6 months of surgery.

DISCUSSION

According to Vuppalapati *et al.*, PA derives its name from the architectural pleomorphism visible on light microscopy. PA is also known as mixed tumor-salivary gland type, a phrase that describes its pleomorphic appearance.[9]

PA being the most common neoplasm of the salivary glands, mainly affects the parotid gland. However, it can also arise from minor salivary glands. When they occur in the minor salivary glands, the most common site is the palate, because the majority of the minor salivary glands are concentrated in the palate followed by the lip, buccal mucosa, floor of mouth, tongue, tonsil, pharynx, and retromolar area. It has been also reported in nasopharynx and parapharyngeal space in rare instances.[3]

PA may occur at any age, but the highest incidence is seen in 3rd, 4th, and 5th decades of life. Females (60%) had a higher incidence of PA when compared to males.[10-12] In the present case, the lesion occurred on the right side of palate in a 54-year-old female patient.

PA arises in the oral cavity as a painless, slow-growing, and firm swelling commonly seen on the posterolateral aspect

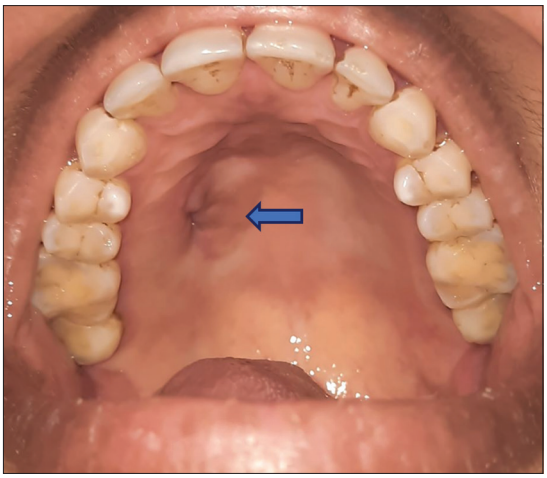

Figure 5: Post-operative intraoral photograph showing healed operated area

of the palate and presents as a smooth, dome-shaped mass.[13] If the tumor is traumatized, secondary ulceration may occur.[10] The palatal swelling in our patient was also painless, dome-shaped, firm with smooth surface, and had a history of slow growth over a prolonged period of 18 years.

Imaging with ultrasound, CT, or MRI may be used depending on the site and size of tumor. However, CT scan with contrast enhancement is an important diagnostic tool as presence of intact fat plane helps in distinguishing benign tumors from malignant ones.[14] In the present case, CBCT was primarily used to determine size and more importantly infiltration of lesion into the surrounding tissue. The lesion was found to be a round to oval hypodense mass, with radiodensity similar to that of soft tissue or fluid having a corticated periphery, measuring about 14.8 mm × 18.5 mm × 19.8 mm. Thinning and superior displacement of both right nasal floor and medial antral wall of right side were noted.

Histologically, the tumor consists of epithelial, myoepithelial, and mesenchymal components arranged in a complex pattern. The epithelial cells arranged in sheets and nests of cells give rise to glandular, ductal structures filled with an eosinophilic coagulum. Squamous metaplasia and keratin pearls may also be present. Myoepithelial cells form a distinct feature of PA, while plasmacytoid myoepithelial cells are significantly found in minor salivary gland tumors. The mesenchymal component shows chondroid, myxoid, and osseous areas.[13] Capsule formation is a result of fibrosis of the surrounding salivary parenchyma that is referred to as a false capsule.[15] In this case, the deeper stroma was characterized by presence of neoplastic islands with diffuse spindle to polygonal cell differentiation along with clear myoepithelial cells. Occasional foci of glandular differentiation with amorphous eosinophilic secretory

deposits were noted. Fibrocollagenous changes and some areas of myxomatous changes were also present in the stroma.

Daryani *et al*. reported a case of PA of the palate and made the following differential diagnosis: hematoma (bluish discoloration), mucocoele, necrotizing sialometaplasia, mucoepidermoid carcinoma, adenoid cystic carcinoma, and polymorphous low-grade adenocarcinoma[13] Sharma *et al*. also reported a similar swelling, where the differential diagnosis were neuroma, palatal abscess, and neurofibroma.[16]

The treatment for PA in palate is wide local excision with the removal of periosteum or bone if it is involved.[17] Because these tumors are radioresistant, radiation therapy is contraindicated.[18] Simple enucleation of this tumor can lead to high local recurrence rate and should be avoided.[19] Although these benign tumors are well encapsulated, resection of the tumor with an adequate margin of apparently normal surrounding tissue is necessary to prevent local recurrence since these tumors are known to have microscopic pseudopod-like extensions into the surrounding tissue due to "dehiscence" in the capsule. The recurrence of this pathosis is attributed to implantation from capsule rupture, islands of tumor tissue left behind after surgery, and its multicentric nature. Therefore, long-term follow-up is required.[20] Mubeen *et al*. reported a recurrence rate of up to 44%.[21] The malignant transformation of the PA has been reported to occur in 2–7% of cases.[22] In this patient, the mucoperiosteal flap was reflected, and the whole tumor mass was excised along with the mucoperiosteum, while the boundary line was localized in the surrounding healthy tissue. There was no evidence of recurrence when the patient was recalled for a periodic check-up in the succeeding 6 months.

CONCLUSION

PA, though a common entity, is still a challenging tumor for pathologist, radiologist, and the surgeon, for which proper diagnostic investigations are essential due to the higher risk of malignancy in minor salivary glands in comparison to tumors of the major salivary glands.

The diverse histological and topographical presentation renders uniqueness to the tumor. The examining clinician and treating surgeon must be aware of its recurrence and malignant potential if incorrectly diagnosed or treated.

Definitive diagnosis lies in the histopathological examination, and surgical excision with wide margins is the treatment of choice. If the bony delimitation between the oral and nasal cavity remains intact, then healing by secondary intention with granulation tissue yields excellent results. Long-term follow-up of the patient is necessary as a considerable rate of recurrence is reported.

Besides, though it is a benign tumor, it can hamper various functions in the oral cavity. Hence, early diagnosis and surgical excision results in complete cure with less or no morbidity.

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Case Report

A Rare Cause of Cervical Swelling: Solitary Neurofibroma

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Abstract

Neurofibroma in the head and neck region is a rare entity and is difficult to diagnose both clinical and radiological. It presents as solitary slowly progressing tumor or as a part of neurofibromatosis disease. We, hereby, report a case of 27-year-old female admitted for a left sided lateral neck swelling, for which the surgical indication was aesthetical impairment. The pathological study was in the favor of neurofibroma. Multiple neurofibroma in the head and neck region may occur in the skin as part of neurofibromatosis and as solitary lesions in the region of the neck. Even they are rare, they should be considered as a differential diagnosis of a neck tumor. Surgery remains the gold standard in the treatment of these types of tumors. It is essential that the surgeon keep in mind the possibility of these tumors as a differential diagnosis of lateral neck swellings.

Key words: Cervical mass, Head and neck, Neurofibroma

INTRODUCTION

A neurofibroma is a benign tumor of peripheral nervous system arising from nerve sheath. Skin (cutaneous neurofibroma) and peripheral nerves (solitary neurofibroma) are common site of its occurrence. These can present sporadically or in association with neurofibromatosis type 1 (NF1), which is an autosomal dominant genetically inherited disease.[1] Neurofibromas arise from Schwann cells which are non-myelinating. These cells exhibit biallelic inactivation of NF1 gene that codes for the protein neurofibromin.[2] The clinical presentation is not specific. Its clinical presentation can be confused with a vascular tumor or malformation, a skin or connective tissue tumor, benign, or malignant.[3] Neurofibroma in the head and neck region is not common. Here, we present one rare case of neurofibroma in the left cervical region.

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CASE DESCRIPTION

A 27-year-old female patient presented to ENT outpatient department with a history of swelling in the left lateral aspect of the neck for the past 10 years. The patient had irrelevant medical history with no known allergies. The swelling was gradually progressive with no associated history of pain. On local examination, there was 8 cm × 4 cm, firm in consistency, non-tender, and non-pulsatile mass in the left lateral aspect of the neck. CECT scan of the neck shows a well-defined thin-walled hypodense lesion measuring 6.3 cm × 8 cm × 10 cm (AP*TR*SI) with numerous internal septae in the left lateral aspect of the neck, medially, and deep to the sternocleidomastoid extending opposite C2 to D3 vertebral levels. Medially, it was displacing the left lobe of thyroid and abutting the left lateral wall of esophagus; however, the fat planes were maintained. Anteromedially, it was also displacing the CCA and ECA and further insinuating into the prevertebral space causing asymmetric bulge in the pharyngeal wall with narrowing of the left pyriform sinus [Figure 1].

Fine-needle aspiration cytology of the mass was undiagnostic and showed blood only. Surgical exploration was planned and the patient was taken for surgery under general anesthesia. Intraoperatively, the mass was grey white

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in color, encapsulated, and glistening measuring 10 cm × 6 cm × 5 cm [Figures 2 and 3]. On the cut surface, it appears mucoid and relatively avascular.

Histopathological examination report showed the tumor mass composed of carrot shredded appearance of stroma with spindle-shaped wavy hyperchromatic nuclei suggestive of benign mesenchymal tumor possibly neurofibroma [Figure 4]. The post-operative period was uneventful. The suture of the wound was removed on the 7th post-operative day and the patient was discharged in satisfactorily condition.

DISCUSSION

A neurofibroma in the head and neck region is very rare. Haller first discovered the carotid corpuscle in 1742. Rodier introduced the term "neuroma" for tumors of the peripheral nerves in 1803.[4] Neurofibromas are slowly progressive benign tumors. These tumors can cause compression on adjacent vital structures or interfere with normal physiology.[5] The presentation of plexiform neurofibroma is uncommon, usually presenting at birth or in the 1st years of life.[6] Neurofibromas usually occur in viscera, solitary cervical presentation is rare. Solitary neurofibromas in cervical region usually present as slowly progressive painless swelling in neck without any other symptoms. Hence, these tumors are commonly ignored by patients, as in our study, neck mass was ignored by the patient for 10 years. Clinical and radiological diagnosis is difficult in these patients due to no specific symptoms and radiological specific features pertaining to this tumor and rarity of this tumor in this location.[7] In our case, specific diagnosis of neurofibroma was not established clinically or radiologically. Recent advances in immunohistochemistry allow increasingly precise diagnosis.[8,9] The majority of neurofibromas are benign, but malignant transformation may occur.[10] Most of these tumors can be quite disfiguring

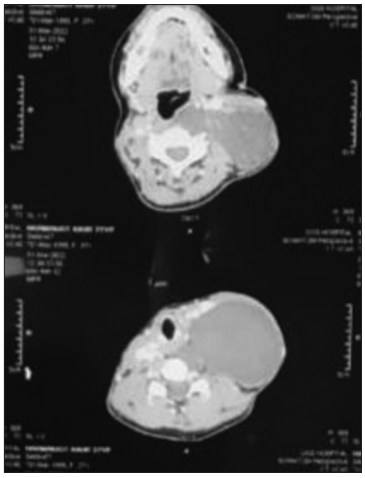

Figure 1: Axial contrast-enhanced computes tomography scan showing the location of tumor in the left lateral aspect of the neck

Figure 2: Surgical exploration of the tumor intraoperatively

Figure 3: Excision of the mass

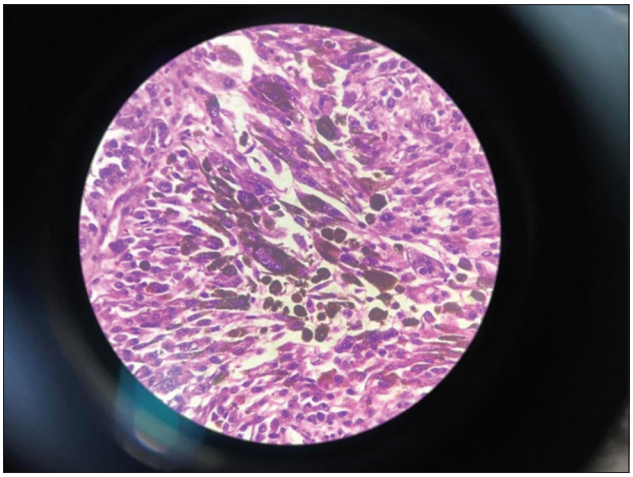

Figure 4: Histopathological slide image showing carrot shredded appearance of stroma with spindle-shaped wavy hyperchromatic nuclei

and are rarely known to cause symptoms ranging from minor discomfort to extreme pain. In our case, the only complaint patient was presenting was the disfigurement. The consistency of the lesion is like a "bag of worms" due to the presence of soft areas interspersed with firm nodular areas. These lesions sometimes are vascular in nature. At histological analysis, a localized and solitary neurofibroma is composed of interlacing fascicles of wavy, elongated cells that often contain abundant amounts of collagen. Rarely, myxoid areas and degenerative regions could be found in neurofibromas. Diffuse neurofibroma contains very uniform, prominent fibrillary collagen. Both localized and diffuse neurofibromas are positive for S-100 protein at immunohistochemical analysis, but this is not a stable finding.[11,12] The treatment of localized and diffuse neurofibromas (not associated with NF-1) is often surgical excision. Sudden increase in size of a previously diagnosed neurofibroma should be viewed with great suspicion of malignant transformation and must be considered for immediate biopsy. The estimated prevalence of malignant transformation varies from 2% to 29%, but they are not well documented in the literature.[13] In our case, tumor was slowly progressing over 10 years, so we did complete excision and sent for histopathological examination.

CONCLUSION

Neurofibroma in the head and neck region is a very rare clinical entity, but it should be considered in the differential diagnosis of head and neck swellings. Multiple neurofibroma in the head and neck region may occur in the skin as part of neurofibromatosis and as solitary lesions in the region of the neck. They are rare tumors with low risk of malignant transformation. If local conditions and the general condition of the patient allow surgery, complete resection of the lesion remains the gold standard in the treatment of these locally invasive tumors.

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We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

All the authors have approved the manuscript and agreed to the submission.

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Case Report

Uterine Artery Pseudoaneurysm: A Rare Cause of Delayed Secondary PPH, Managed with Bilateral Uterine Artery Embolization

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Abstract

Uterine artery pseudoaneurysm is rare cause of delayed secondary postpartum hemorrhage (PPH), but life-threatening condition occurs after traumatic vaginal delivery, dilatation and curettage, cesarean section, or hysterectomy. A 27-year-old female who develops secondary PPH after vaginal delivery was diagnosed to have left side uterine artery pseudoaneurysm on angiography and treated with bilateral uterine artery embolization with PVA particle. The procedure was uneventful. Angiographic embolization is safe and effective method for treating PPH due to pseudoaneurysm in hemodynamically stable patients. Therefore, it should be considered as treatment option before surgical management, in appropriately selected cases.

Key words: Angiography, Bilateral uterine artery embolization, Delayed secondary PPH, Pseudoaneurysm of uterine artery

INTRODUCTION

A pseudoaneurysm of uterine artery is an extraluminal collection of blood with turbulent flow that communicates with parent vessel through a defect in arterial wall. The development of an arterial pseudoaneurysm is rare but reported complication of pelvic surgery, vascular trauma during cesarean section or after uterine curettage, or after traumatic vaginal delivery. After hematoma formation, there is central liquefaction that leaves a cavity with turbulent flow as a result of persistent communication between parent artery and hematoma. The absence of 3 layer arterial wall lining the pseudoaneurysm differentiates it from a true aneurysm which is less common than the pseudoaneurysm.[2] The pseudoaneurysm of uterine artery is an uncommon cause of delayed secondary postpartum hemorrhage (PPH), but it is potentially life-threatening condition. Typically lesions are discovered because the patients have symptoms related to delayed rupture of pseudoaneurysm, causing hemorrhage.[3] Pseudoaneurysm may be asymptomatic or thrombosis may leads to distal painful embolization. The risk of rupture is proportional to the size and intramural pressure. Diagnosis is ultimately based on both Doppler sonography and angiography.[4] Transcatheter uterine artery embolization (UAE) has emerged as highly effective technique for controlling obstetric and gynecologic hemorrhage, including that from pseudoaneurysm. We report a case of uterine artery pseudoaneurysm presenting with the secondary PPH after 23 days of full-term vaginal delivery with cervical tear and managed successfully with PVA foam particle embolization.

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Objective

Proper diagnosis of uterine artery pseudoaneurysm can be established radiologically such as color Doppler and CT scan. Angiography confirms the diagnosis. This condition can be successfully treated by selective UAE.

CASE REPORT

27-year-old female, P2L2A1, day 23 PNC, post full-term vaginal delivery with cervical tear came with c/o excessive bleeding PV since morning on 1/7/17. She gives H/O soakage of 7–8 pads with passage of clots. On examination, the patient was vitally stable, per abdomen-soft, and On Per speculum examination bleeding+, clot +. On per

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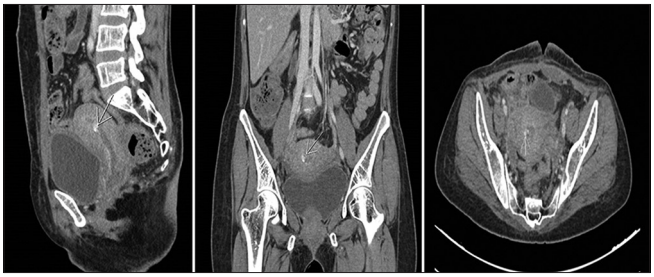
vaginal examination-uterus bulky, postpartum status-internal os closed, Bilateral fornices free, and non-tender. On admission, her Hb was 7.2 g%, beta hcg was done to exclude trophoblastic diseases. All other investigations and coagulation profile was within normal limit. The patient started on higher antibiotics and Inj. Tranexa 1 g tds 2 points whole blood given. On 1/7/17, USG abdo + pelvis suggestive of bulky uterus with thickened and heterogenous endometrium. Findings are likely suggestive of RPOCS. After stabilization, the patient posted for elective check curettage. PAC fitness given. On 10/7/17, elective check curettage was done which was followed by emergency exploratory laparotomy for uterine perforation. Left fundocornual perforation sutured with catgut 1–0 by continuous interlocking suture. Hemostasis achieved. One point whole blood given intraoperatively. Post-operative Hb was 8.7 g%. Postoperatively, no any active bleeding. HPR on 14/7/17 suggestive of products of conception. Post-operative USG on 14/7/17 suggestive of no significant abnormality. On 16/7/17, the patient again complaining of bleeding p/v with 4–5 pads soaked associated with clots since 4–5 h. Urgent USG Abdo + pelvis suggestive of no significant abnormalities. CECT on 16/7/17 suggestive of an enhancing area in endometrial canal near fundus with no abnormally dilated, tortuous vessels. Thickened endometrial canal. Findings are likely suggestive of RPOCS rather than uterine vascular malformation, mild free fluid in pelvis, and mild hepatosplenomegalyone.



One point whole blood given. Post BT Hb was 8.5 g %. On 16/7/17 along with interventional radiology department, the patient posted for UAE. Uterine artery angiography suggestive of left uterine artery pseudoaneurysm. Emergency bilateral uterine artery embolization done at 11 pm with PVA foam embolization particles. Patient withstood procedure well. The patient followed up after 15 days and 1 month. She was asymptomatic [Figure 1].

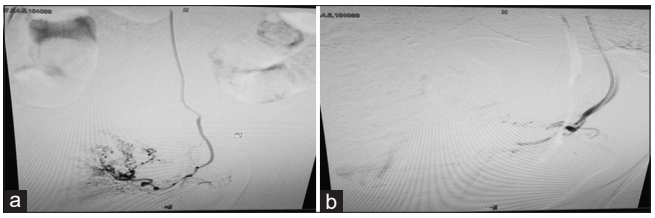


Figure 1: Uterine artery angiography with bilateral uterine artery embolization (a) pre-embolization and (b) post-embolization

DISCUSSION

Post-partum hemorrhage remains a major cause of maternal mortality. Secondary PPH is defined as excessive bleeding starting anytime from 24 h after delivery up to 6 weeks postpartum and most commonly occurs between first 2 weeks. Common causes include RPOCS, subinvolution of placental bed and endometritis.[5] Rare causes include pseudoaneurysm of uterine artery, arteriovenous malformation, and choriocarcinoma. When more common causes have been excluded, pelvic angiography may be performed. UAE can be carried out to control hemorrhage. In 1979, Brown *et al*. reported first case of selective arterial embolization used successfully to treat an extrauterine pelvic hematoma after three failed surgical attempts to controle the bleeding.[6] Since then, arterial embolization has been used successfully to control postpartum bleeding from uterine atony, placenta previa, and vulval and vaginal hematomas. The efficacy and safety of selective arterial embolization artery was evaluated by Pelage *et al*., in woman with delayed secondary PPH. In this series of 14 women, pseudoaneurysm of uterine artery was found in two women.[7] A true aneurysm has all three layers of arterial wall, whereas a pseudoaneurysm does not have all three layers. The differential diagnosis of pseudoaneurysm includes acquired AV malformation, arteriovenous fistulas, and direct vessel rupture. AV malformations are characterized by multiple communications of various sizes between arteries and veins, which can be congenital or acquired. Color Doppler helps to differentiate between them. Color flow Doppler demonstrates "to and fro sign" in neck of pseudoaneurysm and "yin-yang sign" in body of pseudoaneurysm. AV malformations are characterized by marked aliasing on the color flow Doppler and arterialization of venous flow on spectral Doppler evaluation. In our case, the patient developed a pseudoaneurysm on 23 days of full-term vaginal delivery with cervical tear. The treatment was arterial embolization of bilateral uterine artery with PVA foam particles. Angiographic embolization has advantages of decreased morbidity, ability to localize the bleeding site and provide a more distal occlusion than surgical ligation, and preservation of future fertility compared to hysterectomy. Inadequate embolization of pseudoaneurysm due to extrauterine feeding arteries such as internal pudendal artery leading to embolization failure.[2] Hence, bilateral UAE is safe and more advantageous that than unilateral embolization.

CONCLUSION

We conclude that in a woman with unexplained vaginal bleeding after full-term vaginal delivery with cervical tear, a pseudoaneurysm is a potentially life threatening complication and should be considered in differential diagnosis of secondary PPH and can be managed conservatively with bilateral UAE. Although data are scanty, bilateral UAE for obstetric hemorrhage appears to have no increased delirious effect on future fertility and is more effective as compared to unilateral embolization.

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Original Article

Comparative Study of Oral Health Status and Oral Health-Related Habits among Twins in Kodinhi Village, Kerala

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Abstract

Introduction: Researches involving twins are unique in nature as they have the ability to correctly isolate a genetic characteristic and determine its influence on different human traits.

Purpose: The purpose of the study was to compare the oral health status and oral habits of identical and non-identical twins of Kodinhi village, Kerala.

Materials and Methods: The present study conducted among identical and non-identical twins in Kodinhi village, Kerala. The total sample size were 71 pairs of twins aged between 3 and 15 years old, consisting of 142 individuals. Out of 71 pairs, 31 pairs were identical twins and 40 pairs were non-identical. The study compared oral health status and oral habits between the two pairs and also between the two members of a twin pair. The data were analyzed using Chi-square test. Kendall Tau-b Correlation was used to determine the correlation among identical and fraternal twin pairs.

Results: The results showed that all of the study participants had either good or fair oral health status. Among the total, 82.4% had good oral hygiene status and 17.6% had fair oral hygiene. The oral hygiene status of identical and non-identical twins was not statistically significant. The mean decayed missing and filled teeth (DMFT) in identical twins was 2.806 ± 2.023 and 1.944 ± 1.893 in fraternal twins. The mean decayed extracted and filled teeth (DEFT) in identical twins were 3.892 ± 2.973 and 5.021 ± 3.271 in non-identical twins. In both identical and non-identical twin pairs, the DEFT scores were higher than the decayed missing and filled teeth scores.

Conclusion: The correlation rates for oral hygiene status and dental caries were higher in identical twin pairs than the non-identical twin pairs, suggesting considerable evidence that genes play a significant role in the etiology of these traits. In case of habits, a statistically significant difference had obtained only for pencil biting.

Key words: Concordance, Correlation, Fraternal twins, Genetics, Identical twins

INTRODUCTION

In dentistry, we encounter numerous differences in the dentofacial characteristics of individuals, even among family members.[1] Dental characteristics or conditions have multi-factorial inheritance and there is significant evidence in the literature about the influence of genes on the expression of dental and occlusal variables or characteristics which are irrefutable.[2] Dental caries, malocclusion, and periodontal disease are the three most common problem faced in dentistry today. A multifactorial etiology for all three conditions has generally been assumed, with both genetic and environmental contributions to observe variability.[3] One way to determine the respective contribution of genes and environment for a trait is to conduct twin studies.

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Introduction of the twins technique for studying disease pathogenesis is credited to Sir Frances Galton (1876), generally regarded as the father of the twin method. He identified the role of heredity and environment, or "nature and nurture."

Twin studies are a fascinating method of research that it allows disentanglement of the shared genetic and environmental factors for the trait of interest. Researchers can estimate the proportion of variance in a trait attributable to genetic variation, versus the proportion that is due to shared environment or unshared environment.

Kodinhi is a village in Malappuram district of Kerala, India. The village is situated close to the town of Tirurangadi and, as of statistics taken in the year 2016, homes around 3,000 families. The village entered the international spotlight when a survey done by locals found an unusually large number of twin births in the region. The rate of twin birth is several folds higher than the national as well as the global average of twin birth. Although initial estimates put the instance of multiple births at 100 pairs, follow-up surveys found the figure to be closer to 425 pairs (850 individuals) of twins, and two sets of triplets and over 79 pairs of twins within the age group of 0–10 years. Despite several studies being conducted, the exact cause of this phenomenon is yet to be ascertained.[4]

The aim of this study was to assess the oral health status and oral habits among twin pairs of Kodinhi village, Kerala and also to compare those habits between two members of a twin pair.

Although numerous twin studies have been conducted in different parts of the globe on various dental traits, very few studies have been done regarding the oral health status of twins in India. Therefore, this study was conducted to assess and compare oral hygiene status as well as oral habits in identical and non-identical twin pairs.

MATERIALS AND METHODS

Study Design and Sample

A cross-sectional study was conducted among the twins of Kodhini village. The particular study was conducted in 71 pairs of twins, consisting of 142 individuals. Out of 71 pairs, 31 pairs were identical (monozygotic) twins and 40 pairs were non-identical (Dizygotic). They were selected using the convenience sampling method based on the availability of twins. The study protocol was analyzed and approved by the Institutional Review Board. After obtaining consent from the schools, initial identification of twins was done from the school records. On further visits to the school, oral examination of the twin pairs was carried out. Developmentally healthy and cooperative twins belonging to the age group of 3–15 years were included in the study. Medically compromised, reared apart and twins with ongoing orthodontic treatment were excluded from the study.

The steps and procedures of study were explained to both school authorities and parents before conducting the study. Permission and written consent were obtained from the school authorities and parents for examination of the twin children.

In the present study, twins were segregated as monozygous (MZ, identical) and dizygous (DZ, non-identical) on the basis of general facial appearance, hair color, and eye color. This method of zygosity recording is easier and non-invasive, and requires little cooperation from the twin pairs. Comparison of facial appearance is a reasonably accurate means of distinguishing between MZ and DZ twin pairs.[5,6]

Examination of the Children

A proforma was used to record date of birth, gender, demographic details, and oral findings. A single-trained examiner conducted the oral examination using disposable, sterile mouth mirror, and probe. The children were seated upright on a chair and were examined in adequate natural daylight so as to receive maximum illumination.

The oral health status of the twin pairs was measured using decayed missing and filled teeth (DMFT) index, decayed extracted and filled teeth (deft) index, and the simplified oral hygiene index (OHIS and OHIS-M)[7,8]

Oral habits were assessed by asking to the parent and also by intraoral examination and were graded as present or absent.

Statistical Analysis

After completing data collection, data were fed in computer for processing and analysis done using the Statistical Package for the Social Science Version 23. The data were subjected to descriptive statistics such as frequencies, percentage, mean, median, and standard deviation. Qualitative data were compared using Chi-square test and Fischer exact test. Kendall Tau-b correlation coefficient was used to find the correlation between the twin groups.

RESULTS

The particular study was conducted in 71 pairs of twins, consisting of 142 individuals. The age group of the study population ranged from 3 to 15 years. Mean age of the study population was 9.75 years with a standard deviation

of 3.203 years. Out of 71 pairs, 31 pairs were identical twins and 40 pairs were non-identical. Of the identical twins, 15 pairs were male and 16 pairs were female, whereas in non-identical twins, 49 males and 31 females.

Among the study population, 82.4% had good oral hygiene status and 17.6% had fair oral hygiene. None had poor oral hygiene as per the OHI-S Scale [Table 1].

Within the identical twin pairs, a moderate positive correlation obtained for both debris and overall OHI index, whereas a strong positive correlation obtained for calculus index with correlation coefficient, tb = 0.624, 0.679, and 0.806, respectively, with $P = 0.001$ (<0.05) [Table 2].

Within the non-identical pairs, a negligible correlation was obtained for debris, calculus, and overall OHI-S index with correlation coefficient, tb = 0.210, 0.210, 0.261, and $P > 0.05$ [Table 3].

Table 1: Distribution of study subjects based on type of twin and oral hygiene status

Type of twin	Oral hygiene status		Total (%)
	Good	Fair	
Identical twins	48 (77.4)	14 (22.6)	62 (100)
Fraternal twins	69 (86.2)	11 (13.8)	80 (100)
Total	117 (82.4)	25 (17.6)	142 (100)

Chi-square test: 1.878, *P*=0.171 (Not significant)

Table 2: Correlation for oral hygiene status within identical pairs

Index	Kendall Tau-b correlation coefficient	*P*-value	Interpretation
Debris index (DI-S)	0.624	0.001	Moderate positive correlation: Significant
Calculus index (CI-S)	0.806	0.001	High positive correlation: Significant
Simplified oral hygiene index	0.679	0.001	Moderate positive correlation: Significant

Test of correlation: Kendall Tau-b correlation

Table 3: Correlation for oral hygiene status within fraternal pair

Index	Kendall Tau-b Correlation coefficient	*P*-value	Interpretation
Debris index (DI-S)	0.210	0.084	Negligible correlation: Not Significant
Calculus index (CI-S)	0.210	0.154	Negligible correlation: Not Significant
Simplified oral hygiene index	0.261	0.029	Negligible correlation: Significant

Test of correlation: Kendall Tau-b Correlation

The prevalence of dental caries was found to be 69.7% [Table 4]. Among identical twins, 71% had dental caries, whereas among fraternal twins 68.8% had dental caries. This difference was not found to be statistically significant with a Chi-square value of 0.081 at $P = 0.775$ [Table 5]. The mean DMFT in Identical twins were 2.806 ± 2.023 and 1.944 ± 1.893 in non-identical twins. Similarly, the mean deft in identical twins were 3.892 ± 2.973 and 5.021 ± 3.271 in non-identical twins [Figures 1 and 2].

There was a high positive correlation for dental caries within identical twins with a correlation coefficient of 0.767, whereas a low positive correlation obtained for non-identical twins (Correlation coefficient: 0.460) [Table 6].

Among identical twin pairs, 61.3% showed concordance for dental caries, whereas among fraternal twins, only 30 % showed concordance for dental caries. This difference was found to be statistically significant with a Chi-square value of 6.951 at $P = 0.008$ [Table 7].

On comparing the prevalence of various oral habits among the different types of twins, it was found that

Table 4: Prevalence of dental caries in the twin pairs

Dental caries	Frequency	Percent
Present	99	69.7
Absent	43	30.3
Total	142	100.0

Table 5: Distribution of study subjects based on type of twin and presence of dental caries

Type of twin	Dental caries (%)		Total (%)
	Present	Absent	
Identical twins	44 (71.0)	18 (29.0)	62 (100)
Fraternal twins	55 (68.8)	25 (31.2)	80 (100)
Total	99 (69.7)	43 (30.3)	142 (100)

Table 6: Correlation for dental caries index within identical and fraternal pairs

Type of twin	Kendall Tau-b correlation coefficient	*P*-value	Interpretation
Identical twin	0.767	0.001	High positive correlation: Significant
Fraternal twin	0.460	0.001	Low positive correlation: Significant

Test of correlation: Kendall Tau-b correlation

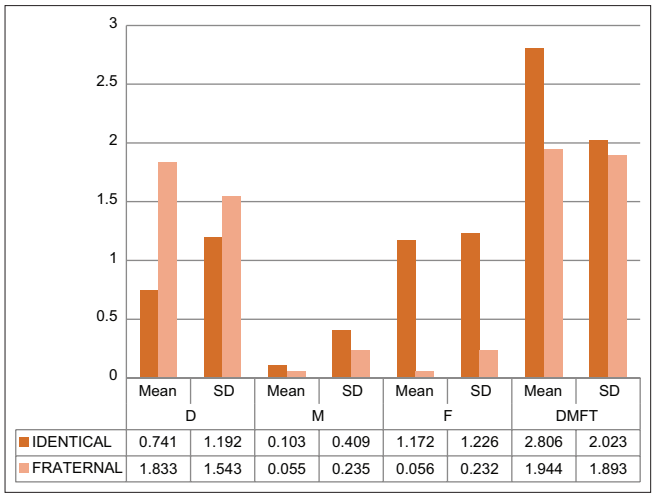

Figure 1: Comparison of decayed missing and filled teeth index between identical and non-identical twin pairs

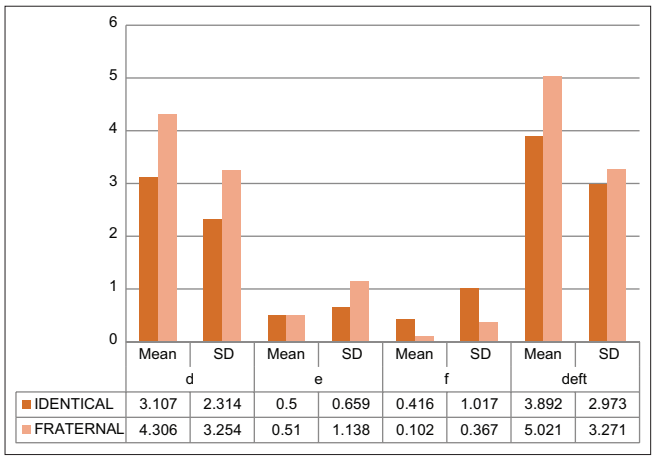

Figure 2: Comparison of decayed extracted and filled teeth index between identical and non-identical twin pairs

Table 7: Distribution of study subjects based on type of twin and concordance for dental caries

Type of twin	Concordant pairs (%)		Total (%)
	Present	Absent	
Identical twins	19 (61.3)	12 (38.7)	31 (100)
Fraternal twins	12 (30.0)	28 (70)	40 (100)
Total	31 (43.7)	40 (56.3)	71 (100)

all the habits were more among identical twins and a statistically significant difference was observed in case of mouth breathing, tongue thrusting, and pencil biting [Table 8].

On comparing the concordance rate of various oral habits among the different types of twins, it was found that for all habits, concordance rate was more among identical twins, but a statistically significant difference was observed only in case of nail biting [Table 9].

DISCUSSION

Twin studies are one of the types of study designs to understand the individual differences by highlighting the role of environmental and genetic causes on phenotypes. Twins are invaluable for studying these important questions, because they disentangle the sharing of genes and environments. The twin design compares the similarity of identical twins who share 100% of their genes, to that of fraternal twins, who share only 50% of their genes.[9]

The present study was conducted in Kodinhi village of Malappuram district, which took the world by surprise when the locals found an unusual and astonishing increase in the number of twins.

The classical twin approach for separating the effects of nature and nurture involves comparing identical (MZ) twins and non-identical (DZ) twins. Differences between MZ twin pairs reflect environmental factors, whereas differences between DZ twin pairs are due to both genetic and environmental factors. Therefore, greater similarities between MZ twin pairs compared with DZ twin pairs can be interpreted as reflecting genetic influences on the feature(s) being studied.[10]

In the present study, the oral hygiene status did not differ between the twin pairs, irrespective of zygosity (monozygosity or dizygosity). This could be due to similar oral hygiene practice followed by the twin pair of children at home.

The observations in the present study are in accordance with the study by Subramaniam *et al*.,[11] where "good" as well as "fair" oral hygiene categories were the most prominent conditions. In his study, he found that oral hygiene was good in about 90% of both MZ and DZ twin pairs. Twin A and twin B of MZ twins showed similar oral hygiene status, with no significant difference between them. This may be due to the shared environment in MZ and DZ twin pairs.

In our study, a significant high positive correlation existed for each of the Debris index, Calculus Index, and overall OHI-S index in Identical twins. In non-identical twins, there was a negligible and non-significant correlation obtained for all the components of OHI-S. It was observed that the correlation rates were higher in identical twin pairs than the non-identical twin pairs, suggesting a strong genetic influence for the same.

Dental caries is a complex, chronic, multifactorial disease, and one of the most common diseases in dentistry along with periodontal disease and malocclusion. Various factors

Table 8: Distribution of study population based on presence of various oral habits and type of twin

Oral habits	Type of twin	Frequency (Percentage)	Test of significance	*P*-value	Impression
Mouth breathing	Identical	18 (29)	χ^2=8.459	0.004	Significant
	Fraternal	8 (10)			
Thumb sucking	Identical	6 (9.7)	Fischer exact test	0.066	Not significant
	Fraternal	2 (2.5)			
Tongue thrusting	Identical	29 (46.8)	χ^2=10.391	0.001	Significant
	Fraternal	17 (21.2)			
Bruxism	Identical	2 (3.2)	Fischer exact test	0.192	Not significant
	Fraternal	0 (0)			
Nail biting	Identical	20 (32.3)	χ^2=2.773	0.096	Not significant
	Fraternal	16 (20)			
Pencil biting	Identical	16 (25.8)	Fischer exact test	0.001	Significant
	Fraternal	4 (5.0)			

Table 9: Distribution of study population based on concordance for various oral habits and type of twin

Oral habits	Type of twin	Concordant pairs (%)	Test of significance	*P*-value	Impression
Mouth breathing	Identical	31 (100)	Fischer exact test	0.126	Not significant
	Fraternal	36 (90)			
Thumb sucking	Identical	31 (100)	Fischer exact test	0.986	Not significant
	Fraternal	39 (97.5)			
Tongue thrusting	Identical	26 (83.9)	χ^2=0.175	0.676	Not significant
	Fraternal	32 (80)			
Bruxism	Identical	31 (100)	Fischer exact test	0.986	Not significant
	Fraternal	39 (97.5)			
Nail biting	Identical	30 (96.8)	Fischer exact test	0.035	Significant
	Fraternal	31 (77.5)			
Pencil biting	Identical	29 (93.5)	Fischer exact test	0.690	Not significant
	Fraternal	36 (90.0)			

such as diet, saliva, oral bacteria, and tooth morphology have been attributed to the occurrence of dental caries, suggestive of environmental as well as genetic influence in its etiology. The earlier twin studies have shed light on this fact (Bretz *et al*., 2005; Conry *et al*., 1993).[12]

In both identical and non-identical twin pairs, the deft scores were higher than the DMFT scores. This may be due to more number of twin pairs included in the 6–11 age groups and probably be due to their similar dietary pattern and oral hygiene habits. There was a significant high positive correlation obtained for dental caries in identical twins, whereas only a significant low positive correlation was existed in non-identical twins.

In this study, we also investigated the concordance for dental caries between the twin pairs. About 61.35% of identical twins showed concordance for dental caries, whereas among non-identical twins, only 30% showed concordance and the results were statistically significant.

Twin studies by Bretz *et al*, Conry *et al*., and Lovelina *et al*.[13] on dental caries have shown that genetic as well as environmental factors play a significant role. Mansbridge[14] studied the caries incidence in 96 MZ and 128 DZ twins. The study showed that dental caries experience had a greater similarity between MZ twins than DZ twins, whereas unrelated pairs of children showed less similarity. This observation was supported by other studies that showed dental caries resemblance which was higher among MZ twins. The MZ twins showed a greater correlation than the DZ twins, which is in accordance with this study.

Majority of the earlier studies failed to establish a significant genetic contribution for phenotypes. Twins reared apart model allows a more precise assessment of the inherited component controlling the phenotype. Regarding caries development, two twin studies using twin pairs reared apart demonstrated that MZ twins had higher similarity in incidence of dental decay than DZ twins, despite the fact that the individuals have been raised in different families, communities, and/or even countries, there is a strong argument in favor of the existence of a genetic contribution (Boraas *et al*., Conry *et al*.).[15]

Only few reported studies are available regarding the oral habits among twins. On comparing the prevalence of various oral habits among the different types of twins, it was found that all the habits were more among identical twins and a statistically significant difference was observed in case of mouth breathing, tongue thrusting, and pencil biting, suggesting a possible genetic contribution for these

habits. In contrary to this, Panchmal *et al*.,[16] in his study in the same twin population in 2013, found that mouth breathing, bruxism, and thumb sucking were the most prevalent oral habits.

This study presented a comprehensive over view of the oral health-related habits among twins. There were only few previous studies reported in the literature regarding the habits and practices related to oral health in twins. Studies had reported similarity in dietary pattern and oral health status among twins.[17,18] The findings of our study suggest that identical twins exhibited a correlation in certain oral health-related behaviors and habits which suggest a strong genetic and environmental relationship.

Some of the habits reported in this study like tongue thrusting, thumb sucking, and bruxism seen in identical twins suggest a positive relation of the genetic traits of the individuals. Other habits such as pencil biting and nail biting could have a genetic influence or they may have been adopted as a result of socio-environmental influence.

Although co-twin analysis control for genetic and shared environmental factors, it is always possible that residual confounding by environmental factors may exist. On the other hand, if identical twins and non-identical twins are more similar with respect to these environmental risk factors, we may attribute confounding by an environmental factor to a genetic factor.

CONCLUSION

Like many of the population based studies, this study also has some limitations. Our study was an attempt to compare the oral health status and oral habits of identical and fraternal twins of Kodinhi village, a village known for its unusual number of twin births. The following conclusions were drawn from the study:

- Identical twin pairs showed a higher correlation rate for oral hygiene status and dental caries than the non-identical twin pairs, suggesting considerable evidence that genes play a significant role in the etiology of these traits
- It was found that all the habits were more among identical twins and a statistically significant difference was observed in case of mouth breathing, tongue thrusting, and pencil biting, suggesting a positive relation of the genetic traits of the individuals
- For concordance of oral habits, a statistically significant difference had obtained only for pencil biting. Other habits such as thumb sucking and nail biting could have been a genetic influence or they may have been adopted as a result of socio-environmental influence.

Clinical Significance of the Study

Identification of genetic risk factors for common dental problems would help to reduce costs associated with treatment and prevention of the most frequent oral diseases. Similarly, genetic disorders are attended with less importance than other diseases. There is a lack of knowledge between genetic diseases and its prevention among the general population. Therefore, better understanding of the genetic etiology of the diseases can facilitate early detection in high-risk groups. General awareness should be raised by the government policies about cost-effective genetic diseases and genetic counseling technique, and genetic therapy should be made affordable by the community level.

Along with emerging genome and molecular researches, twin studies surely shed light on how environmental and genetic factors influence on human traits and behaviors.

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Original Article

A Study on Prevalence of Anemia among Female Medical Students of Kerala

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Abstract

Introduction: Iron deficiency anemia is one of the most common nutritional disorders in women and children. The prevalence of anemia in India ranges from 19.13% to 52.5%. The risk factors include low socioeconomic status, menstruation, nutritional status, hand hygiene, and worm infestations. Untreated anemia can lead to morbidities including delayed menarche, increase in infections, low birth weight, increase in infant mortality rate, and maternal mortality rate. This study aims at understanding the prevalence of anemia among female medical students of Kerala.

Materials and Methods: Participants were included following the inclusion and exclusion criteria. Body mass index (BMI) was calculated as the WHO guidelines after recording the height and weight of the candidates. The hemoglobin was estimated using Sahli's acid hematin method and correlated with the BMI of the students.

Results: Seventy-eight female students participated in the study out of which 19 were underweight, 51 had normal BMI, and eight were in obesity category. Forty-four students had hemoglobin above 13 g/dL. Among the 19 students who were underweight, six were found to be anemic and among the students with normal BMI, 26 were found to be anemic. The prevalence of anemia among the underweight category was 56.25% and in students with normal BMI, 51% were found to be anemic.

Conclusion: The reason for students developing anemia is related to improper knowledge, attitude, and practice toward dietary habits, menstrual irregularities, and possibly occult parasitic infestations. It is essential that appropriate preventive measures such as health education, lifestyle modification, education about nutrition, and nutritional supplementation be carried out to reduce short-term and long-term morbidities among female undergraduate medical students.

Key words: Anemia, Body mass index, Female gender, Hemoglobin, Iron deficiency anemia, Sahli's acid hematin method

INTRODUCTION

Anemia is one of the most common nutritional disorders in women and children. As per the recent WHO estimates, 29.9% of women in the age group of 15–49 years are anemic world wide and 39.8% children until the age of 10 years is anemic.[1] The most common reason for anemia worldwide is the iron deficiency anemia. The normal hemoglobin percentage in males is 13 g/dL and females is 12 g/dL. The anemia is classified based on the hemoglobin percentage as mild (Males: 11.0–12.9 g/dL and females: 11.0–11.9 g/dL), moderate (8.0–10.9 g/dL in both genders), and severe (<8.0 g/dL in both genders).[2,3] Studies have been conducted in different regions of India showing the prevalence of anemia was 52.5% in Madhya Pradesh, 37% in Gujarat, 41.1% in Karnataka, 85.4% in Maharashtra, 21.5% in Shimla, 56.3% in Uttar Pradesh, 77.33% in Andhra Pradesh, 58.4% in Tamil Nadu, and 19.13% among college students in Kerala.[4-12] The major risk factors identified from literature include low socioeconomic status, blood loss during menstruation, nutritional status, hand hygiene, and worm infestation. In India, helminthic infestation is very common which can lead to chronic blood loss which, in turn, results in anemia.[13] Anemia if left untreated can lead to various adverse effects. As per the documented literature physiologically it can cause delay in onset of menarche and increase in incidence of infections due to impairment in immune system. If the anemia is ignored on a long term and in the event of pregnancy may

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lead to increased incidence of low birth weight, increase in infant mortality rate, and maternal mortality rate.[14]

Medical students on the other hand with better knowledge about nutrition and access to healthcare would be expected to have better health indices but in practice it is noticed that many students especially female students are seen to have varying grades of anemia. The studies done for detection of anemia exclusively in female medical students suggest that around 19.13–35.1% of them suffer from varying degrees of anemia. The reasons attributable to this include poor eating habits, meal skipping, snacking, increasing fast food consumption among medical students added to the long schedules of studying, and family adoption visits and early clinical exposure postings of the new curriculum-based medical education prescribed by the National Medical Commission.[12,15-17]

Hemoglobin and its Methods of Estimation

The hemoglobin molecule is a tetramer consisting of two pairs of similar polypeptide chains called globin chains. To each of the four chains is attached heme which is a complex of iron in ferrous form and protoporphyrin. The major (96%) type of hemoglobin present in adults is called HbA and it has 2 alpha-globin chains and two beta-globin chains ($\alpha 2\beta 2$). The gene that codes for the formation of α-globin chains is located on chromosome 16 and that which codes for the formation of β-globin chains is on chromosome 11. In adults, a minor amount of HbA2 ($\alpha 2\beta 2$) is also present and constitutes <3.5%. Various methods are available for estimation of hemoglobin in the laboratory. Most commonly used methods are based on development of color. These include Sahli's acid hematin method, cyanmethemoglobin method, oxyhaemoglobin method, and alkaline hematin method. Among these methods, the common ones are Sahli's acid hematin method and cyanmethemoglobin method. Sahli's acid hematin method uses the simple principle wherein blood is mixed with N/10 HCl resulting in the conversion of Hb to acid hematin which is brown in color. The solution is diluted until its color matches with the brown colored glass of the comparator box and concentration of Hb is read directly.[18] Cyanmethemoglobin method is the internationally recommended method for determining hemoglobin. Here, the blood is diluted in a solution containing potassium cyanide and potassium ferricyanide. Potassium ferricyanide converts Hb to methaemoglobin which is converted to cyanmethemoglobin (HiCN) by potassium cyanide. The absorbance of the solution is, then, measured in a spectrophotometer at a wavelength of 540 nm or in a colorimeter using a yellow green filter.[19] Oxyhaemoglobin method converts Hb to oxyhaemoglobin by reaction with ammonia and the color of the solution is measured in a photocolorimeter. Finally, the Alkaline hematin method where blood is converted to alkaline hematin by addition of alkali such as sodium hydroxide and the color measured in a colorimeter at 540 nm.[20] Among these methods, we selected the Sahli's acid hematin method as it is easy to perform, quick, and inexpensive, can be used as a bedside procedure and can be done by students under supervision as it does not require technical expertise.

MATERIALS AND METHODS

The study was conducted in Azeezia Institute of Medical Sciences and Research, Kollam district of Kerala state between March 2022 and September 2022 among the female undergraduate Medical students belonging to 2021 batch all above the age of 18 years. Candidates with history of anemia and other comorbid diseases such as hypothyroidism, chronic renal diseases, bleeding disorders, known cardiac ailments, hypertension, hyperthyroidism, and surgery in the recent past were excluded from the study. The weight in kg was measured using a standard digital weighing scale with Krups weighing machine wearing light clothes and without shoes. The machine was calibrated to nearest 0.1 kg. The height in centimeters using stadiometer was recorded. Subjects were asked to stand in Frankfurt plane position. Body mass index (BMI) was calculated as weight in kilogram divided by the square of the height in meters. BMI <18.5 kg/m^2 is categorized as underweight, between 18.5 and 24.9 kg/m^2 as normal, 25.0–29.9 kg/m^2 as pre-obesity, 30.0–34.9 kg/m^2 as obesity class I, 35.0–39.9 kg/m^2 as obesity class II, and more than 40 kg/m^2 as obesity class III or morbid obesity. The students were demonstrated on the method of hemoglobin estimation using Sahli's acid hematin method and were allowed to perform the test under supervision. Blood was collected using aseptic finger prick method. N/10 HCl was taken into the graduated hemoglobin tube up to mark 2 g%. 20 μL blood was collected in hemoglobin pipette under aseptic precautions without air bubbles. Tip of pipette was wiped off to avoid blood adhering to it. Blood was transferred immediately to N/10 HCl in hemoglobinometer tube. Pipette was rinsed several times by drawing N/10 HCl without foaming. After mixing the contents were left undisturbed for 10 min. The maximum conversion of hemoglobin to acid hematin occurs now and gives a brown color to the mixture. Then, distilled water was added to dilute the acid hematin and continuously mixed with stirrer until the color matched the standards in the comparator. Reading was taken at eye level under natural day light after lifting the stirrer up and the reading was recorded in g/dL. The anemia is classified based on the hemoglobin percentage as mild in males with hemoglobin of 11.0–12.9 g/dL and in females when the reading is between 11.0 and 11.9 g/dL. Moderate anemia

was when the hemoglobin levels were between 8.0 and 10.9 g/dL and severe anemia when the hemoglobin was <8.0 g/dL. The results were analyzed on Microsoft Excel and Chi-square tests. Students with mild anemia were given dietary counseling after getting a detailed history on socioeconomic status, dietary habits, menstrual history, and history of passing worms. Students with moderate and severe anemia were counseled and advised medicine consultation for work up and pharmacotherapy of anemia.

RESULTS

A total of 78 female students participated in this study. As per our protocol, height and weight of all students were measured as described earlier. Out of the 78 students, 19 students were found to be underweight. Fifty-onestudents were having normal BMI and eight students were found to be in the pre-obesity category as per the recent WHO criteria. Out of the 78 students, 44 were having a hemoglobin of more than 13 g/dL. Thirty-four students were observed to have anemia of varying degrees. Among the 19 students who were underweight, six students were found to be anemic. Four students had mild anemia with hemoglobin values ranging from 11.0 to 11.9 g/dL and two students had moderate anemia ranging between 8.0 and 10.9 g/dL. Among the students with normal BMI, 26 students were found to be anemic. Twenty students had mild anemia, followed by five students having moderate anemia and one student having severe anemia. Among the pre-obesity students, two students who were found to be anemic had severe anemia. The prevalence of anemia in this group of undergraduate female medical students was 43.5%. Among the underweight students the prevalence of anaemia was found to be 56.25%. Among the students with normal BMI, 51% were anemic and in the students with pre-obesity, 25% were severely anemic.

DISCUSSION

Anemia is one of the most common nutritional deficiencies found in developing countries. Iron deficiency anemia is the most common type of anemia in India. This anemia is more among the female gender especially in the reproductive age group. The incidence of anemia among the female undergraduate medical students in this study was 43.5% and about 70% of students had mild anemia. Most of the students belong to the middle class and upper middle class socioeconomic class as per the modified Kuppuswamy socioeconomic status scale for the year 2022[21] and, hence, poverty cannot be ascertained as a cause for anemia in these students. The mean hemoglobin percentage was 11.9 g/dL and the mean BMI was 20.8.

In this study, Sahli's acid hematin method was used as it is easy to perform, quick, and inexpensive, can be used as a bedside procedure, and does not require technical expertise and even students can be easily trained. This method has certain disadvantages as well. It is less accurate compared to cyanmethemoglobin method. All hemoglobins (oxyhaemoglobin and sulfhemoglobin) are not converted to acid-hematin, and hence, the value of hemoglobin obtained is less than the actual value. The color of acid hematin develops slowly. Color of acid hematin fades with time and dilution must be done exactly after 10 min when the color development is maximum. Individual variation in matching of color is seen. If the matching point is passed, the whole procedure has to be repeated. Color of glass in the comparator box tends to fade with time.

The medical students of the current generation are following the new Competency Based Medical Education introduced by the erstwhile Medical Council of India. As the socioeconomic status does not play a considerable role in causation of anemia, we started looking at other factors leading to anemia. Few students had given history of menstrual irregularities in the discussion after performing the hemoglobin estimation. On further discussions on the dietary intake, it was seen that many students were skipping breakfast, increased snacking, and fast-food consumption. The present study showed that the prevalence of anemia among undergraduate female medical students was 43.5%. It is essential that appropriate preventive interventions such as health education, lifestyle modification, and nutrition supplementation be carried out in this population so as to reduce the morbidity of anemia and its complications in high-risk settings.

CONCULSION

Female Students in the medical Profession are not exempt from suffering nutritional disorders like anaemia. This is attributable to change in dietary pattern, lifestyle and increase in intake of fast foods among college going children. Adding to the woes is the prevalence of menstrual irregularities among students in this age group. The need of the hour for prevention of anaemia is regular counselling on good dietary habits and menstrual health. These simple steps will go a long way in preventing short term and long-term complications related with iron deficiency anaemia.

Limitations

The sample size was limited and the exact estimate can be obtained using a larger sample size.

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Original Article

The Link between Negative Life Events and Depression

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Abstract

Introduction: Depression is a widespread mental condition that affects people in India and all across the world of different ages, genders, and socioeconomic positions. Stressful life events (SLEs) can occur before or concurrently with other mental or physical health issues.

Aim: The study aims to assess the severity of depressive symptoms, the presence of SLEs, and the correlation between SLEs and the severity of depression.

Methods: A cross-sectional study was conducted in a tertiary care hospital from March 2021 to March 2022. One hundred and fifty individuals diagnosed with major depressive disorder according to International Classification of Diseases-10 were evaluated for the severity of depressive symptoms and the occurrence of SLEs within the past 1 year using the Hamilton depression rating scale and presumptive SLEs scale.

Results: One hundred and fifty depressed people between 18 and 62 were enrolled. The mean age was between 37.9 ± 11.9 years. Women were found to experience major depressive disorder compared to men $p<0.05$. It was more prevalent in the 2nd decade of life. As the severity of SLEs increases, the severity of depressive disorder also increases – a significant positive correlation between the total presumptive SLEs and the Hamilton depression rating scale.

Conclusion: The severity of the depressive disorder is higher among women, especially in middle age. In addition, as the severity of SLEs increases, the severity of depressive disorder also increases.

Key words: Depressive disorder, Stressful life events, Mental condition, Negative thoughts

INTRODUCTION

The old and traditional Latin words depressant and deprimere are used to denote depression. Deprimerie is essentially described as "pressing down," because de means "down" and primerie means "to push." The word essentially refers to feeling "pushed down," which is sometimes described as feeling "sad," "blue," or even plain "down" or "depressed." It was simply a phrase for a decline in mood or spirit when it was first used in 1665 to describe a mental or emotional disease.[1] Thus, it appears that the primary depressive experience, or dysphoria in psychiatric words, is personal.

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Depression is a widespread mental condition that affects people in India and all across the world of different ages, genders, and socioeconomic positions. Estimates place the prevalence of MDD at 3.2–4.7% worldwide and predict that by 2030, unipolar depression will surpass bipolar illness as the second-leading source of disease burden.[2,3]

Stressful life events (SLEs) can occur before or concurrently with other mental or physical health issues. They are frequently associated with the development of major depression in adults[4,5] and adolescents.[5] Or, they might exacerbate depression symptoms that already exist.[13] According to the kindling theory

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(Post, 1992), initial bouts of mood disorders are more likely than subsequent episodes to be brought on by acute psychosocial stressors. The later episodes may take place even in the absence of stress or with only minor stressors.[14] Few people react to such stressful life circumstances more negatively than others, and comprehending the nature of this connection has emerged as an important research topic.[6,7]

Life events are "discrete occurrences interrupting a person's routine, resulting in a significant change and readjustment."[8] These occurrences could encourage someone to face the problem with optimism and productivity, or they might hurt that person's well-being. Numerous life experiences – both good and bad – are important determinants of someone's psychological health. The previous studies have shown that dependent life events are more connected with depression than independent life events. A dependent event is likely to occur as a result of the respondent's activity (for example, being fired from a job), but an independent event occurs regardless of the person's behavior or mental state (Williamson *et al.* 1995).[9]

Researchers have been considering the role of life stresses in developing many physical and mental illnesses for decades. According to research, SLEs are linked to a disease's eventual emergence.[10,11] Stressful life circumstances have consistently been linked in the literature to subsequent major depressive episodes. "A significant proportion of people with depressive disorder say that SLEs occurred just before the beginning of depression."

Aim

The study aims to assess the severity of depressive symptoms, the presence of SLEs, and the correlation between SLEs and the severity of depression.

MATERIALS AND METHODS

It is a cross-sectional study carried out at Sree Balaji Medical College and Hospital, Chennai. Patients visiting the hospital's outpatient department for 1 year, from March 2021 to March 2022, were taken up for the study. Eligible participants included those diagnosed with major depressive disorder according to International Classification of Diseases (ICD)-10 criteria and registered in the psychiatry department of Sree Balaji Medical College and Hospital. The sample size was 150, and the convenient sampling method was selected. Participants who were currently experiencing depressive symptoms, aged 18–65 years of both genders, and were willing to give informed written consent to participate were included in the study. Participants who were unwilling to give informed written consent and patients with cognitive impairment, intellectual disability, psychosis, hypomanic, manic, and mixed symptoms were excluded from the present study.

Data Collection and Analysis

The investigator-assessed patients registered in the psychiatry OPD and verified by the treating consultant. Those fulfilling the diagnostic criteria of the depressive disorder according to ICD-10 were approached for participation in the study. Those willing to participate in the study, fulfilling the inclusion, and exclusion criteria after obtaining informed written consent, were enrolled. A self-constructed and semi-structured pro forma was used to collect the sociodemographic details. History of psychiatric and medical illness, family history, and personal history was specifically enquired for. Hamilton depression rating scale (HAM-D) was used to assess the severity of the depressive disorder. A person's response to the first 17 questions is used to compute their overall score. Normal scores range between (0–7), mild (8–13), moderate (14–18), and severe depression (19–22).

The presumptive SLEs scale (PSLES) was used to check for stressful events. It consists of 51 life events that an average Indian is likely to encounter. It provides a quantitative estimate of the presumed stressors as experienced.

SPSS version 25 was used to carry out the statistical analysis. Demographic data involving continuous variables were represented as percentage distribution or frequencies and mean with standard deviation. An independent *t*-test was used to compare the mean between two continuous variables. The Chi-square test was used for comparing categorical variables. $P < 0.05$ was considered significant, and linear correlation analysis was performed for presumptive SLEs and the severity of the depressive disorder.

RESULTS

Age, Gender, and Marital Status and Education and Profession

One hundred and fifty depressed people between 18 and 62 were enrolled. The mean age was between 37.9 ± 11.9 years. Most of the study sample comprised females (65.3%, $n = 98$) males accounted for (34.7%, $n = 52$). About 73.2% of the study population were married ($n = 110$), 15.3% were unmarried ($n = 23$), 5.3% were separated ($n = 8$), 5.3% were widowed ($n = 8$), and 0.67% were divorced ($n = 1$).

Among the study population of depressed individuals, 4.0% ($n = 6$) were illiterate, 8.0% ($n = 12$), and 10.0% ($n = 15$) had completed primary school and middle school,

respectively. In addition, 38.0% (n = 57) had completed high school, 8.7% (n = 13) had a professional degree, 4.7% (n = 7) possessed a diploma degree, and 26.6% (n = 40) were graduates.

A high percentage of the population were housewives (38.7%, n = 58), followed by professionals (14.0%, n = 21), skilled laborers (13.3%, n = 20), semi-professionals (11.3%, n = 17), semi-skilled laborers (6.0%, n = 9), unemployed (5.3%, n = 8), students (2.7%, n = 4), housekeeping department (0.7%, n = 1), and retired (0.7%, n = 1).

SLEs

Over the previous year, the average total presumptive SLEs score was 145.3 ± 76.4, with a range of 44–487 (95% CI: 133.1–157.6). Therefore, the average number of presumptive SLEs experienced by each individual was estimated to range between 1 to 8 events. The frequency and percentage distribution of individuals who experienced SLEs during their lifetime are seen in the table below.

It was observed that a sizable percentage of the study population (n = 52, 34.7%) had two SLEs. (28.7%, n = 43) Individuals with three SLEs, one SLE was seen in (n = 28, 18.7%), five SLEs (n = 5, 3.3%), and a few people had seven to eight SLEs [Table 1].

The study sample of depressed individuals was, further, classified based on total presumptive SLEs scores: scores up to 40 were perceived as no stress, scores ranging between 41 to 200 as mild-to-moderate stress, and more than 200 as severe stress.

The entire study population had gone through SLEs, a significant proportion (n = 124, 82.7%) experienced mild or moderate SLEs, and the rest of the people (n = 26, 17.3%) underwent severe SLEs [Table 2].

Depressive Disorder

The average Hamilton score for depression was 15.9 ± 3.5 (ranging from 9 to 24; 95% CI: 15.4–16.5). Similar to the presumptive SLEs classification tool, the Hamilton depression rating scale is employed to categorize the severity of depression. Scores were substantiating mild (8–13), moderate (14–18), and severe (19–22) depression, respectively. Study results revealed that (n=81, 54%) individuals had moderate depression, followed by (n=36, 24%) who had mild, severe depression (n=26, 17.3%), and very severe depression (n=7, 4.7%).

Correlation Studies

SLEs with depression

The assessment of the association of SLEs with the severity of depressive symptomatology in the study population revealed a significant statistical correlation (χ^2 = 65.9, P = 0.000) between SLEs and the severity of depression [Tables 3 and 4].

These results signify that most persons with mild-to-moderate scores of SLEs correspond with mild-to-moderate severity of the depressive disorder. Similarly, as the severity scores of SLEs elevate, it also elevates the severity of depression. Hence, as the severity of SLEs increases, depression also increases, representing the positive relationship between SLEs and depression.

Therefore, a positive relationship between the studied variable has been validated. Correlation analysis was performed to delineate the relationship between the total presumptive SLEs score against the Hamilton depression rating scale score. The analysis established a significant positive correlation (correlation co-efficient = 0.8; P = 0.000*) between the total presumptive SLEs and the Hamilton depression rating scale [Figure 1].

DISCUSSION

Our study included 150 participants, of whom 98 (65.3%) were women and 52 (34.7%) were men. This accords with the previous research showing a higher incidence of depressive disorder in females. Compared to men, women reported more distress, anxiety, and depressive symptoms (Wfiams and Spitzer, 1983; Vitaliano *et al.*, 1989; and Zeidner and Ben-Zur, 1994).[12-14] According to earlier studies, women were more likely than males to experience a depressive disorder.[15]

For various biological factors, including genetic susceptibility, hormonal changes associated with various aspects of reproductive function, and excessive sensitivity to these changes in hormone levels in the brain systems that mediate depressive states, women are thought to be predisposed to depression. As a result of reproductive events such as infertility, miscarriage, oral contraceptives, and hormone replacement treatment, women have been reported to experience depression. Women can experience depression at various phases of the menstrual cycle (premenstrual dysphoric disorder, depression during pregnancy, postpartum depressive conditions, and menopausal depression). According to some research, women are more likely to experience depression due to psychosocial factors like role stress, victimization, sex-specific socialization, internalization coping style, and low socioeconomic status. In addition, women are more susceptible than men to depression brought on by stress.[16]

Table 1: Classification of depressed individuals based on frequency total presumptive SLEs score (*n*=150)

Number of SLEs	Study population frequency	Study population percentage
1	28	18.7
2	52	34.7
3	43	28.7
4	16	10.7
5	5	3.3
6	3	2.0
7	1	0.7
8	2	1.3

SLEs: Stressful life events

Table 2: Classification of depressed individuals based on total presumptive SLEs score (*n*=150)

Category of stress	Frequency	Percentage
No stress	0	0
Mild/moderate stress	124	82.7
Severe stress	26	17.3

SLEs: Stressful life events

Table 3: Classification of study individuals according to the severity of depression (*n*=150)

Depression levels	Frequency	Percentage
Mild depression	36	24
Moderate depression	81	54
Severe depression	26	17.3
Very severe depression	7	4.7

Table 4: Correlation of SLEs with severity of depression in the study population

Depression levels	SLE, *n* (%)		χ^2	*P*-value
	Mild/moderate stress	Severe stress		
Mild depression	36 (100%)	0 (0%)	65.9	0.000
Moderate depression	75 (92.6%)	6 (7.4%)		
Severe depression	13 (50.0%)	13 (50.0%)		
Very severe depression	0 (0.0%)	7 (100%)		

SLEs: Stressful life events

The Severity of Depressive Disorder

According to the Hamilton depression rating scale (HAM-D), patients were given a score based on the severity of their depressive symptoms. They were, then, categorized as mild (8–13), moderate, severe (14–18), or severe depression (19–22), and scores higher than 22 indicate very severe depression. According to the study's findings, moderate depression affected 54% (n = 81) of people, 24% (n = 36) were affected by mild depression, 17.3% (n = 26) suffered from severe depression, and 4.7% (n = 7) were very severely depressed.

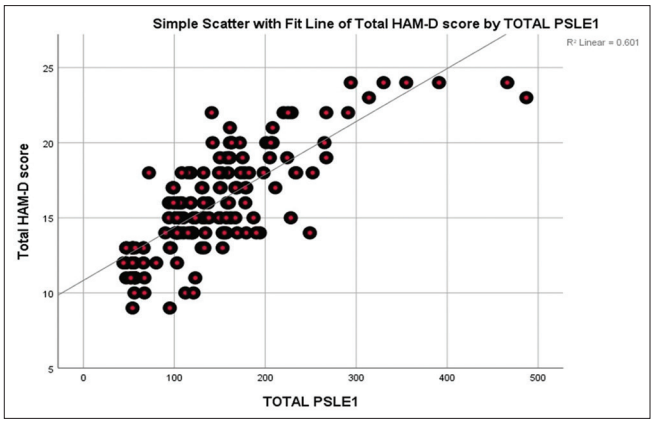

Figure 1: Correlation of total presumptive stressful life events score with Hamilton depression rating scale score

SLEs

The study group's average SLEs score was estimated to be (145.3 ± 76.4) with a range of 44 to 487. They were also studied for the frequency of their occurrence, that is, the number of SLEs a person experienced during the past 1 year. There was one event at the very least, and eight at the very most. Two SLEs were encountered by most of the population (n = 52, 34.7%). Few people (11) had more than five significant life events in the last year. Patients were also categorized based on the sum scores of all life events during the previous year, which was correlated with the severity of depression.

Correlation of Severity of Depression with SLEs

Our research indicates that at least one SLE occurred for the study sample in the previous 12 months. Our study showed that patients with mild-to-moderate depressive disorders reported mild to moderately SLEs. Individuals with severe and very severe depression go through extremely hard life situations.[17]

The severity of depressive symptoms also increases along with the severity of life events. According to the study, there is an association between the degree of depression and stressful situations (2=65.9, P = 0.000).

According to studies from the past, there is a link between SLEs and subsequent illnesses. Researchers have examined their significance in the origins of physical sickness for the past 30 years, but there has been less convincing evidence of a connection.

Today, biological characteristics brought on by a person's genetic makeup are referred to as "diathesis." However, the term "diathesis" has been broadened to include social and cognitive predispositions that could raise someone's risk of getting a disease like depression.

When the diathesis is present, the degree of stress will determine how the disorder manifests; as stress rises, the risk for the disorder in those with the diathesis also rises (Ingram and Luxton, 2005).[15]

When compared to persons who do not experience any SLEs, a study by Muscatell *et al.* found that the majority of severe stressful events (such as the death of a spouse or family member, divorce, and financial loss) lead to the development of depressive symptoms within 6 months of their occurrence. Those who experience SLEs are at a higher risk of developing depression.[18]

The onset of depressive disorder was strongly and significantly correlated with SLEs. Kendler *et al.*[17] studied the association of depression with dependent and independent life events occurring in an individual's life. The study published a positive correlation between life events and the onset of major depressive disorder. The results of past studies correspond to our study, which shows a positive relationship between the frequency of SLEs and the severity of depression.

PSLES scores for SLEs and clinical depressive symptoms were shown to be closely associated in our study ($\chi^2 = 65.9$, $P = 0.000$), which resembled the results of Sokratous *et al.*[16] ($\chi^2 = 40.06$, $P < 0.001$). Evidence suggests a linear relationship between depression and the severity and quantity of unpleasant events. Among university students in Cyprus, Sokratous *et al.*[16] explored the frequency of depressive symptoms and their correlation with the quantity and intensity of self-reported SLEs. The prevalence of clinically substantial depressive symptoms, as evaluated by the CES-D, and SLEs, as assessed by the total number and score of SLEs, measured by the LESS, were found to be significantly linked.

Our study results correspond with the results of Muscatell *et al.*[18] Bonde *et al.*[19], Feizi *et al.*[14], Young *et al.*[20] Leggett *et al.*[21], Chen *et al.*[22], Tehrani *et al.*[7], Mandelli *et al.*[4], Hammen *et al.*[5], and Monroe *et al.*[23] which have published results about the association of SLEs with depressive disorder.

CONCLUSION

The severity of depressive disorder is higher among women, especially in middle age. In addition, as the severity of SLEs increases, the severity of depressive disorder also increases.

Limitations

It is a hospital-based sample and not truly representative of the community. In addition, the study sample was relatively small and recruited from a single center. Therefore, there is no comparative group for the study sample.

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Original Article

Outcome of Intramedullary Interlocked Nailing in Closed and Gustilo Anderson Grade I Tibial Fractures

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Abstract

Introduction: Most common long-bone fracture is tibial shaft fracture. Open fracture wounds must be continually evaluated by the operating surgeon. The first step is to assess the damage to the soft tissues, which often extends past the opening in the skin. Foreign bodies, dead muscle, dead bone, and soft tissue must be removed. Treatment of tibial diaphyseal fractures has always been tough because of its subcutaneous location, and there may be severe soft tissue injuries and many of these can be open fractures.

Methods: In this Study attempt has been made to critically evaluate the outcome of closed intramendullary interlocked nailing in tibial fractures regarding union, functional healing and the complications of the procedure. In this study we have selected patients of closed and open grade-I tibial shaft fractures in patients of age more than 16 years, treated by closed IMIL nailing at Rajendra Institute of Medical Sciences, Ranchi. Study was done from November 2020 to November 2022. Total 30 cases were included. All the cases were followed up till the union of fracture was achieved. They were examined clinically, radiologically and functionally.

Results: According to Karlstrom & Olerud functional scoring system 18patients had excellent overall functional results, 9 had good results, 2 had acceptable results only one patient had poor result on account of her old age and poor health condition.

Conclusion: Statically locked, reamed intramedullary nailing remains the standard treatment for displaced tibial shaft fractures. Closed intramedullary interlocked nailing for acute tibial fractures gives excellent results in closed and grade-I open fractures if done judiciously and with proper technique.

Key words: Interlocked nailing, Diaphyseal fracture, Gustilo Anderson classification, Tibial shaft fracture

INTRODUCTION

A tibial shaft fracture occurs commonly due to trauma, commonly in middle-aged and young people[1] less prevalent in children and older people.[2] The most common site of long bone fractures is tibial shaft because of its superficial location.[3] Most common long-bone fracture is tibial shaft fracture.[4]

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Open fracture wounds must be continually evaluated by the operating surgeon.[5] The first step is to assess the damage to the soft tissues, which often extends past the opening in the skin.[6] Foreign bodies, dead muscle, dead bone, and soft tissue must be removed. Copious irrigation continues as long as foreign material and dead tissue flow out of the wound. If the fracture is multifragmentary, small bony fragments without muscle attachment are removed. Avoid soft-tissue stripping of fracture fragments.[7] High-pressure irrigation systems may force bacteria back into the tissues and these bacteria will emerge later and cause infection.[8] The location where the injury occurred may also add bacteria as in the classic "barnyard injury." Appropriate antibiotics are given for these.[9]

Treatment of tibial diaphyseal fractures has always been tough because of its subcutaneous location, and there

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may be severe soft tissue injuries and many of these can be open fractures.[10]

In this study, attempt has been made to critically evaluate the outcome of closed intramedullary interlocked nailing in tibial fractures regarding union, functional healing, and the complications of the procedure.[11]

Intramedullary nail fixation remains the treatment of choice for unstable and displaced tibial shaft fractures in the adult.[12] The goals of surgical treatment are to achieve osseous union and to restore length, alignment, and rotation of the fractured tibia.[13] Intramedullary nailing carries the advantage of minimal surgical dissection with appropriate preservation of blood supply to the fracture.[14] Moreover, the surgical implant offers appropriate bio-mechanical fracture stabilization and acts as a load sharing device allowing for early post-operative mobilization.[15] Recent advances in nail design and reduction techniques have expanded the indications for intramedullary nail fixation to include proximal and distal third tibial fractures.[16]

This procedure has 2 benefits, one is it controls the rotational stability of fracture parts, better correction of angulation deformity, lesser damage to soft tissue covering of bone thereby preserving vascularity of the bone, decreased blood loss, may be used not only in the mid shaft fractures but also in proximal and distal fractures.[17] Therefore, it is popularly accepted as primary method of fixation in Grade I open fractures.[18] However, this method is associated with complications like general complications: Deep Vein Thrombosis, Pulmonary Embolism, Pneumonia, Infections, etc.

In distal third tibial shaft fractures undergoing intramedullary nail fixation, adjunct fibula fixation may allow for achieving and maintaining fracture reduction of the tibia.[19] However, there remains the concern of wound complications from the additional incision in the area of traumatized tissue.[20] We therefore suggest using adjunct fibula fixation cautiously.[21]

Good outcomes and reproducible results can be achieved with intramedullary nail fixation of tibial shaft fractures.[22] The reported union rates of intramedullary tibial nailing vary among different studies.[23] With contemporary implants and appropriate surgical techniques, union rates above 90% can be expected.[24] Tibial shaft fractures that fail to heal following intramedullary nail fixation typically respond well to exchange reamed nailing procedures.[25] Proximal locking helps to keep the nail from backing out into the knee if it loosens or the fracture telescopes.[26] Neil *et al.* used open technique of intramedullary nailing with distal locking first because this process help to control the nail and able to check drill in proper position through guide wire.[27] Compression is achieved through distal locking first and back slapping. It is commonly used method in tibial shaft fracture.[27]

Anterior knee pain is a commonly reported complication after intramedullary nailing of tibial shaft fractures.[28] Potentially contributing factors may include traumatic and iatrogenic damage to intraarticular structures, injuries to the infrapatellar branch of the saphenous nerve, thigh muscle weakness secondary to pain-related neuromuscular reflex inhibition, fat pad fibrosis leading to impingement, reactive patellar tendonitis, bending strain exerted by the nail on the proximal part of the tibial bone, and proximal protrusion of the nail.[29] In an attempt to address the etiology of anterior knee pain after intramedullary nailing, transtendinous approaches have been compared to paratendinous approaches. The previous studies suggested that transtendinous may be associated with a higher incidence of postoperative knee pain.[30] However, prospective randomized clinical data has not shown any significant difference between the transtendinous and paratendinous approach. Jones *et al.* reported no statistical differences with regards to anterior knee pain between patients undergoing suprapatellar versus infrapatellar nailing.[31] However, the authors reported that there was trend toward greater symptomatic knee pain in the infrapatellar group.[32] Due to hinge joints at the ankle and knee, no adjustment occurs for rotatory deformity after a tibial shaft fracture.[33] Non union, infection and delayed-union and are common complications after open tibial shaft fractures.[34] Rapid restoration of bone continuity and early callus formation is the main aim for diaphyseal fracture of tibia.[35]

MATERIALS AND METHODS

In this study, we have selected patients of closed and open Grade-I tibial shaft fractures in patients of age more than 16 years, treated by closed IMIL nailing at Rajendra Institute of Medical Sciences, Ranchi. Study was done from November 2020 to November 2022. Total 30 cases were included in the study. All the cases were followed up till the union of fracture was achieved. They were examined clinically, radiologically, and functionally.

Inclusion Criteria

The following criteria were included in the study:

1. Patients from either sex of above 16 years.
2. Isolated tibia fracture.
3. Closed or open Gustilo Anderson grade-I, fractures of both bones leg.
4. All those fractures of tibia which are 7 cm distal to knee and 4 cm proximal to the ankle joint.

5. Unilateral or bilateral tibial fractures.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patient <16 years of age.
2. Any associated fracture in the same or opposite lower limb.
3. Fractures proximal to 7 cm of tibia or distal to 4 cm of tibia.

Open fractures were classified according to the classification of Gustilo and Anderson. Other investigations done included a complete blood count with ESR, prothrombin time, activated partial thromboplastin time, blood urea nitrogen, serum creatinine, random blood sugar, blood grouping and matching, and chest X-ray.

Management

After the patients came to emergency, appropriate dose of analgesic were given to patients to relieve pain and above knee plaster of paris (POP) back slab was given to the patient.

Injuries to the surrounding skin and soft tissues, such as fracture blisters, skin abrasions, or skin tenting, must be recorded. Open fractures must be identified and appropriate tetanus update and antibiotics should be initiated immediately on the initial presentation. A comprehensive neurovascular examination must be performed and documented.

The evaluating surgeon should maintain a high suspicion for an associated compartment syndrome and serial clinical examinations are required in these patients.

It was tried that the patients be operated as early as possible depending upon condition of the patients of fractured limb as well as systemic conditions. Preoperatively, the patients were given a broad-spectrum antibiotic, generally a third generation cephalosporin and dose repeated after 6–8 h postoperatively.

Operative Technique

The patients were operated under the spinal anesthesia as considered appropriate by the anesthetist. A tourniquet was applied over the thigh and pressure raised to 250 mm Hg most of the time depending on systolic blood pressure.[36] However for nailing, tourniquet was avoided.[37]

Establishing an accurate starting point continues to play a crucial role in any intramedullary nailing procedure. In general, the more proximal the fracture, the more lateral the entry point should be. Ideal starting point lies at the anterior edge of the tibial plateau and just medial to the lateral tibial spine. Moreover, Tornetta *et al.* reported on a safe zone with a width of 22.9 mm ± 8.9 mm which allows for a safe nail insertion without the risk of damage to the adjacent articular structures.[38] Traditionally, the starting point for intramedullary nailing of tibial shaft fractures has been established through an infrapatellar approach either by splitting the patellar tendon (transtendinous approach) or alternatively by dissecting just adjacent to the patellar tendon (paratendinous approach). Nailing in the semiextended position has recently gained significant attention in the orthopaedic literature.[39] Nailing in the semiextended position using a medial parapatellar approach has been suggested by Tornetta and Collins as a method to avoid apex anterior deformities.[40] Recent reports have adopted this concept suggesting tibial nailing in the semiextended position using a suprapatellar portal and nail insertion through the patellofemoral joint.[41]

The procedure is performed with the knee flexed approximately 15–20°. An approximately 3 cm longitudinal incision is made about one to two fingerbreadths above the patella. The quadriceps tendon is split in a longitudinal fashion and the patellofemoral joint is entered through further blunt dissection. A cannula system with a blunt trochar is then inserted through the patellofemoral joint to establish the starting point at the junction of the anterior cortex of the proximal tibia and the articular surface. The starting point is established under fluoroscopic guidance using a 3.2-mm guide pin strictly adhering to the fluoroscopic landmarks described above. A multiholed guide pin sleeve is available and may allow for fine adjustments of the starting point. The remaining surgical procedure including reaming of the canal and tibial nail insertion is performed through the cannula system which allows for safe protection of the surrounding soft tissues and articular structures. The semiextended leg position potentially facilitates the fracture reduction in particular in proximal third tibial fractures with the typical apex anterior deformity.[42] Suprapatellar nailing in the semiextended position may also represent an alternative to the traditional infrapatellar approach when soft tissue injuries around the infrapatellar area make the placement of surgical incisions undesireable.[43]

Reduction

Placement of the tibial nail alone does not result in adequate fracture reduction and appropriate fracture alignment must be maintained throughout the reaming process and nail placement.[44] While application of longitudinal traction typically results in improved fracture alignment through ligamentotaxis, the simple application of manual traction by itself may not al- ways achieve an anatomic fracture alignment.[45] The universal distractor can be used as an additional reduction tool. The universal distractor may

assist in maintaining length and alignment.[46] Careful attention must be paid to the placement of the Schanz pins. These are placed from the medial side into the proximal and distal fragment away from the planned position of the tibial nail.[47] Similar to the universal distractor, two-pin external fixation can be used to obtain and maintain length and alignment during intramedullary nailing of tibial shaft fractures. Blocking screws (or "poller" screws) have been popularized by Krettek *et al.*[48] The purpose of blocking screws is to narrow the canal in the metaphyseal area and to substitute a deficient cortex.[49] The blocking screws are placed prior to the reaming process and nail placement. Blocking screws are typically placed in the short, articular fragment and on the concave side of the deformity.[50] For instance, the typical deformity of a proximal third tibia fracture is characterized by a valgus- and apex anterior deformity.[51] To overcome the valgus deformity, a blocking screw can be placed in an anterior to posterior direction into the lateral portion of the proximal fracture fragment (i.e., on the concave side of the deformity). This blocking screw is used to guide the nail medially and thus prevents a valgus angulation.[52] Similarly, the apex anterior deformity can be overcome by a blocking screw that is placed in a medial to lateral direction in the posterior portion of the proximal fragment (i.e., on the concave side of the deformity).[53]

However, in our study, para patellar approach or splitting of patellar tendon was used, reaming was done in most of the cases.[54] Length was measured by measuring tape on uninjured limb.

Rotational malalignment was avoided by aligning the iliac crest, patella, and the second ray of foot.[55] Distal locking was done using free hand technique and proximal locking was done through the jig. All wounds were closed and antiseptic dressing was done.

Post-operative Management

Limb elevation was done and above knee POP posterior slab was applied. Surgical wound dressings and drain removal (if any) was done 48 h after surgery. A post-operative radiograph was taken for evaluation of surgery. Partial weight bearing was started when there was clinical evidence of fracture healing, usually about 3 weeks. Full weight bearing was started when there was radiological evidence of fracture union, usually about 3–4 months. Karlstorm and Olerud 36-point clinical grading system and radiological evaluation of leg was used during follow-up of patients.[56] This system evaluated the patients both subjectively and objectively and thus gave a comprehensive picture of the patient's condition. An overall result of excellent, good, acceptable, or poor was determined according to the following criteria:

- Excellent - Score of 3 in all the factors listed above.
- Good - Score of 2 or more in all the factors listed above.
- Acceptable - Score of 1 in one factor and scores of 2 or 3 in all other factors.
- Poor - Score of 1 in more than one factor.

RESULTS

30 cases of closed and open Grade-I tibial shaft fractures were included in the study. This study is based on observations from 30 cases. The mean age of patients was 40.5 years. Transverse fracture was the most common occurring in 19 (63.3%) patients followed by Oblique fractures in 7 (23.3%) patients. 25 patients (83.3%) had closed tibial shaft fractures while 5 (16.6%) patients had an open grade I fracture. Reaming was done in 20 (66.6%) patients while unreamed tibial nail was put in 10 patients. 10 mm size nail was used in most (15) patients. Dynamic locking was done in 20 (66.6%) patients and static locking was done in 10 patients. No patients had valgus or varus deformity radiologically of more than 15°. Most (85%) patients needed no immobilization. 4 patients had an above knee POP slab while 2 patient had a below knee POP slab. Most patients (21) started partial weight bearing within 9 weeks post-surgery followed by 5 patients between 9 and 12 weeks and another 4 patients after 12 weeks post-surgery. The average interval between surgery and partial weight bearing was 10 weeks (3–32 weeks). Most patients (25) started full weight bearing within 24 weeks after surgery. Four patients started full weight bearing between 24 and 36 weeks and only one patient on account of old age started full weight bearing after 36 weeks. Dynamization was done in 5 patients. 27 patients had complete union while only 3 had delayed union.

According to Karlstrom and Olerud functional scoring system all patients had excellent results of pain evaluation. 27 patients had a score of 3 and only 3 patients had a score of 2 with regards to the previous sports activity. 19 patients had a score of 3, 7 patients had a score of 2 and only 4 patients had a score of 1 with regards to walking capacity. 18 patients had a score of 3, 9 patients had a score of 2 and only 3 patients had a score of 1 with regards to work limitation. No patient had any obvious deformity at follow-up. No patient had any limb length discrepancy at follow up. 90% patients had less than 10 degrees loss of knee motion while only 3 had between 10 and 20° loss of motion. All patients had almost full range of ankle movement. All patients had almost full range of subtalar motion. 26 (86.6%) patients had at least 140 degree range of movement, 4 (13.4%) patients at least 100 degree range of movement and no patient had less than 100 degree range of motion at the knee joint.

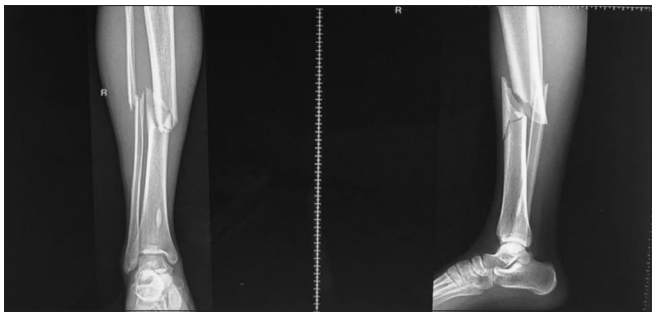

Figure 1: Case 1- fracture mid shaft tibia along with fibula at same level

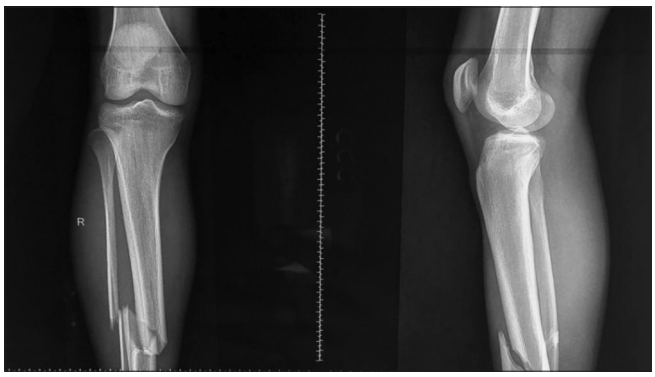

Figure 2: Case 1 (another radiograph)

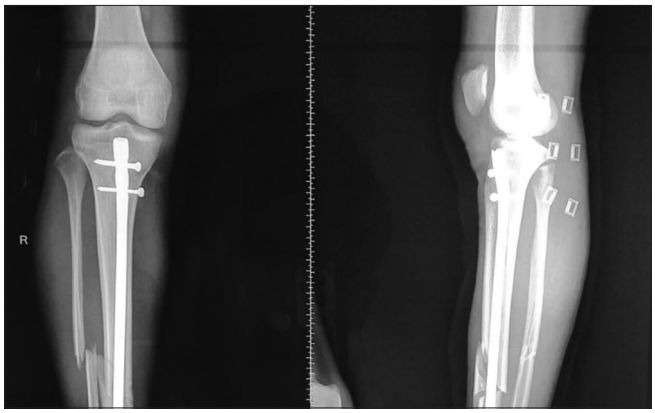

Figure 3: Post op X-ray of case 1

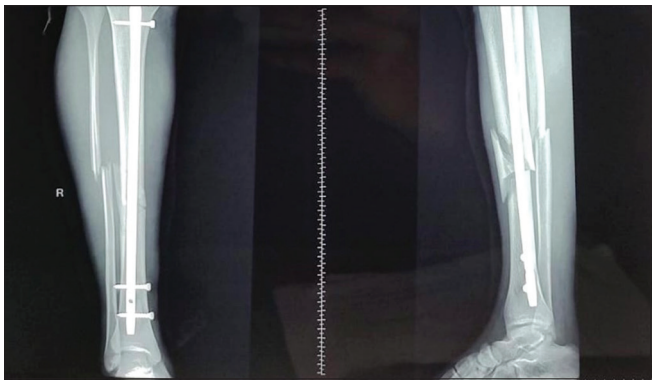

Figure 4: Another post op X-ray of case 1

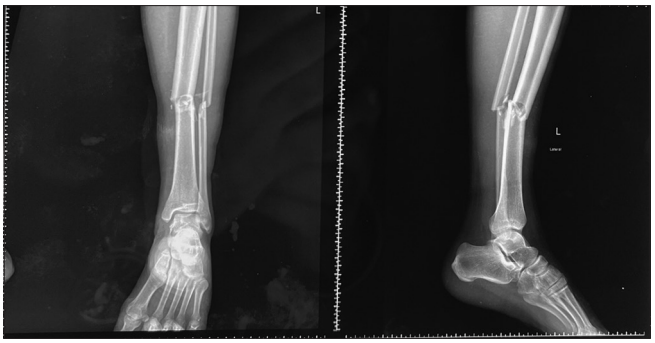

Figure 5: Case 2 fracture shaft of tibia and fibula

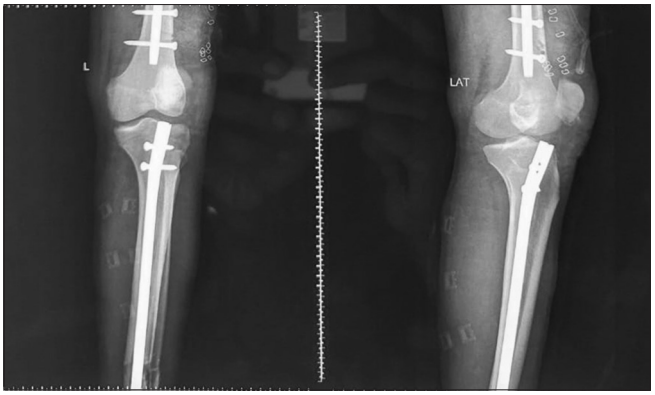

Figure 6: Post op X-ray of case 2

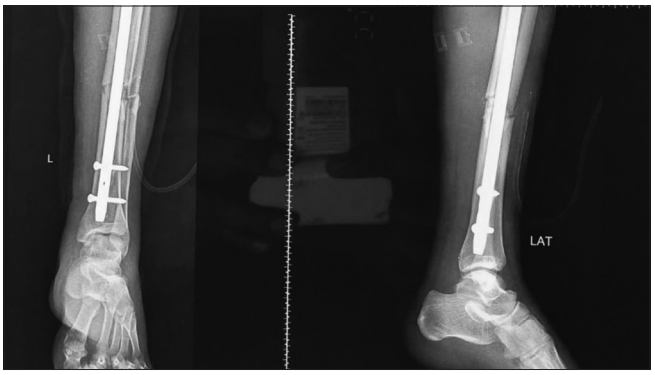

Figure 7: Post op X-ray of case 2

Most patients had bony union radiologically by 24 weeks and 4 between 24 and 36 weeks. Only three patients had infection at proximal insertion site at follow-up. 1 patient had a broken implant at 24 weeks when full weight bearing was done. Later on he was treated with an above knee POP cast with implant left in situ. The bone united at 6 months later. The proximal half of the broken nail was removed thereafter. No patient required secondary surgeries for surgical complications. According to Karlstrom and Olerud, functional scoring system 18 patients had excellent overall functional results, 9 had good results, 2 had acceptable results. and only one patient had poor result on account of her old age and poor health condition.

Figure 8: Case 3

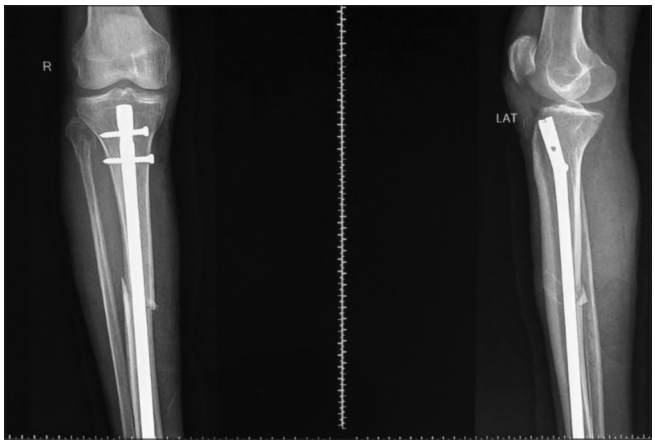

Figure 9: Post op X-ray of case 3

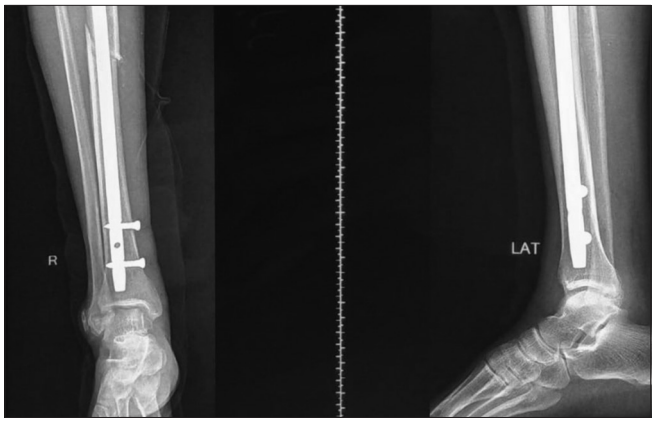

Figure 10: Post of x ray of case 3

DISCUSSION

Shaft of tibia fractures are the most common long bone fractures in adults and happen due to high-energy trauma. Its site and also that the anteromedial border is subcutaneous puts the bone susceptible to injury.[57] In particular, the younger patient population seems to be at high risk for the development of a compartment syndrome.[58] The diagnosis of a compartment syndrome should be based on clinical findings including pain, neurovascular changes, swelling of the muscle compartments, and pain increase with passive toe stretch. Thus, compartment syndrome remains a clinical diagnosis.[59] Measuring of intracompartmental pressure through a pressure needle has been suggested as a useful tool and may play a role, in the obtunded patient when the availability of clinical data points is limited.[60] To obtain reliable data, the intracompartmental pressures should be measured in all four muscle compartments and in different locations within the respective muscle compartments. A differential pressure (diastolic blood pressure minus compartment pressure) of <30 mmHg has been suggested to be indicative of a compartment syndrome.[55]

Surgical treatment of tibial shaft fractures is debatable because good results are also there by closed reduction and casting as shown by Sarmiento *et al.*[55] However, with conservative treatment, loss of reduction which causes malunion and nonunion is also common.[57] The main objections to surgical treatment are mainly contributed to plate osteosynthesis because plating of the tibial shaft fracture causes high risk of infection.[59] After the invention of the interlocked nail there was a milestone achieved in the nailing technique as it provided the rotational stability. Furthermore, the dynamization of the nail was not problem because of slot for dynamic nail are given proximally.[61] Recently, these kinds of fractures are treated with anatomical restoration of alignment, stable, and rigid internal fixation with rotational stability and early weight bearing.[62] The aim of operative treatment is to obtain a proper anatomical alignment, early knee mobilization exercises, and early weight bearing even before the bony union is achieved.[63]

At many trauma centers reamed tibial nailing is preferred over unreamed tibial nailing.[64] However, the issue of reamed versus unreamed tibial nailing has been discussed controversially. It has been suggested that reamed nailing allows for placement of larger size nails allowing for increased biomechanical stability and potentially improved fracture healing.[65] In contrast, it has been reported that intramedullary reaming results in significant compromise of the endosteal blood supply which may potentially limit the biologic healing response at the fracture site.[66] Moreover, the concern remains that the reaming process may increase the risk of fat embolization and pulmonary failure.[67]

Most surgeons prefer reamed intramedullary tibial nailing over unreamed nailing. However, both reamed and unreamed intramedullary nailing can be suggested as

acceptable standard techniques and good outcomes can be achieved with both of these methods.[67]

CONCLUSIONS

Statically locked, reamed intramedullary nailing remains the standard treatment for displaced tibial shaft fractures. A correct starting point remains a crucial part of the surgical procedure. Suprapatellar nailing in the semi-extended position has been suggested as a safe and effective procedure. Open reduction techniques should be considered if anatomic fracture alignment cannot be achieved by closed means. Favorable union rates above 90% can be achieved by both reamed and unreamed intramedullary nailing.

This study consisted of mainly middle aged patients, mostly males. Age and sex did not changed the results significantly. High velocity road traffic accidents were the main cause of injury. Distal 1/3rd tibial shaft fractures were most common followed by middle 1/3rd, upper 1/3rd being the least common. Transverse fractures topped the study followed by oblique and spiral fractures. No obvious correlation of days between injury and operation with outcome of results was seen. However, delay in operation causes greater soft tissue swelling making the management more difficult. In comminuted fractures, rigid fixation like closed intramedullary interlocked nailing gave better functional results as it is a minimally invasive procedure which does not require opening of the fracture site thus hematoma is not drained. Moreover, the length and rotation of the limb are maintained and at the same time there is angular correction. The purpose of interlocking screws in tibial shaft fractures is to prevent shortening and malrotation. The introduction of interlocking screws has expanded the indication for intramedullary tibial nailing to more proximal and distal third tibial shaft fractures with metaphyseal involvement. In fractures involving the metaphyseal area, interlocking screws become more important in maintaining axial alignment due to the absence of a strong nail-cortex interface.

However, we also had our share of unsatisfactory results with regards to angulation deformity, delayed union, malunion, and non-union. Knee pain was the most common complication seen. This was due to slightly protruding proximal end of the nail, which was found to be jetting out just beneath the patellar tendon, which can be attributed to poor nailing technique. In the distal and proximal third there was some degree of angulation. Hence, the surgeon should be careful about the alignment while locking proximally and distally.

Finally, we conclude that closed intramedullary interlocked nailing for acute tibial fractures gives excellent results in closed and Grade-I open fractures if done judiciously and with proper technique. Moreover, it offers significant benefits to the patient in the form of short hospital stay, early range of motion exercises, also partial weight bearing can be started early, so both function and healing of fracture goes side by side and thereby, consequent good functional results were achieved in a majority of these fractures.

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Original Article

Immunohistochemical Study of the Expression of Myofibroblasts in Metastatic Lymph Nodes of Oral Squamous Cell Carcinoma

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Abstract

Aim: Role of myofibroblasts in the stroma of oral squamous cell carcinoma (OSCC) is well studied, but activation of this entity in the metastatic lymph nodes is faintly known. The present study aims to evaluate the expression of myofibroblasts and to characterize the distribution pattern of these cells in metastatic lymph nodes of OSCC.

Materials and Methods: Sixty formalin-fixed paraffin-embedded tissue blocks of cervical lymph nodes (levels I, IIA, IIB, and III) of resected OSCC samples were examined immunohistochemically by anti-rabbit monoclonal α-smooth muscle actin. The expression of myofibroblasts was compared with clinicopathological parameters of OSCC.

Results: All metastatic lymph nodes of OSCC showed presence of activated myofibroblasts and expression of these cells was significantly ($p < 0.5$) increased in relation to pattern of invasion (POI) and grade of invasion in lymph nodes.

Conclusion: Myofibroblasts in lymph nodes may play a major role in establishing and supporting the growth of metastases in lymph nodes. The prognostic significance of myofibroblast expression in different POI in lymph nodes should be further investigated.

Key words: Alpha-smooth muscle actin, Lymph node, Metastasis, Myofibroblast, Oral squamous cell carcinoma

INTRODUCTION

Regional lymph node metastasis plays a pivotal role in initial diagnosis, staging, and management of oral squamous cell carcinoma (OSCC) and is the single most important prognosticator for afflicted patients.[1,2] Approximately 30% of patients with intraoral SCC present with positive regional lymph nodes.[3] Metastasis is driven by intrinsic factors such as the genetic and epigenetic characteristics of the cancer cells and critically affected by extrinsic factors mediated by the tumor microenvironment.[4] Tumor microenvironment (TME) consists of the extracellular matrix, carcinoma-associated fibroblasts, immune-inflammatory cells, and endothelial cells.[5,6] Cancer-associated fibroblasts (CAFs) are tumor-associated fibroblasts with myofibroblast-like phenotype which is the main component of the tumor stroma, and these have recently been paid a large amount of attention due to the prominent roles that they play in cancer development, progression, and metastasis.[7-10] A variety of growth factors and inflammatory chemokines secreted by stromal myofibroblasts are involved in the remodeling of the tumor stroma, the regulation of the motility of cancer cells, and the induction of tumor cells toward phenotypes that are more resistant to chemotherapy.[11,12] Some studies have reported that stromal myofibroblasts are associated with a poor prognosis in oral cancers.[13] Although the role of myofibroblasts in the stroma of primary tumor is well studied, only indirect observations currently suggest that modification of the stromal architecture such as activation of myofibroblasts takes place during metastatic

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conditioning of the lymph node microenvironment.[14] A conditioning of the microenvironment in lymph nodes is required making them receptive and supportive metastatic niches for disseminating tumor cells.[15,16]

Modified immunological responses and remodeling of the vasculature are the most studied tumor-induced pre-metastatic changes in the lymph node microenvironment that promotes metastasis, whereas modification of the stromal architecture such as activation of myofibroblasts in the cervical lymph node metastases of OSCC is not studied widely. In normal lymph nodes, myofibroblasts are not found within the body of the lymph node, whereas studies indicate that myofibroblastic reactions are evident in metastatic disease of breast cancer and metastatic lymph nodes of colorectal carcinoma.[17,18]

Although the knowledge of myofibroblasts participation in lymph node metastasis is evolving, there is little work investigating the expression of myofibroblasts in metastatic lymph nodes of OSCC. Hence, the present study aims to investigate the expression of myofibroblasts in metastatic lymph nodes of OSCC.

MATERIAL AND METHODS

Study Sample

The retrospective observational study comprised 50 metastatic and ten non-metastatic formalin-fixed paraffin-embedded tissue blocks of cervical lymph nodes dissected from radical neck dissection of histopathologically confirmed OSCC were obtained from the tissue archives of Department of Oral Pathology and Microbiology, SCB Dental College and Hospital, Cuttack. All the patients were informed about the study and written consent was obtained. The study was approved by the Institutional Research Ethics Committee vide no-IEC/SCBDC/012/2018.

Hematoxylin and Eosin Staining

All the samples were stained with hematoxylin and eosin with standard protocol and viewed under a light microscope to confirm and validate the prior diagnosis and grading. Lymph node parameters such as pattern of invasion (POI) and lymph node invasion grades were also evaluated as follows.

POI in Metastatic Lymph Nodes (as per Chandavarkar *et al.*[19])

Cords – Metastatic cells invade lymph nodes in the form of thin cords (Figure 1a and b), Islands – Metastatic cells invade lymph nodes in the form of small and large islands (Figure 1c and d),

Total replacement – Total lymph node effacement (Figure 1e and f).

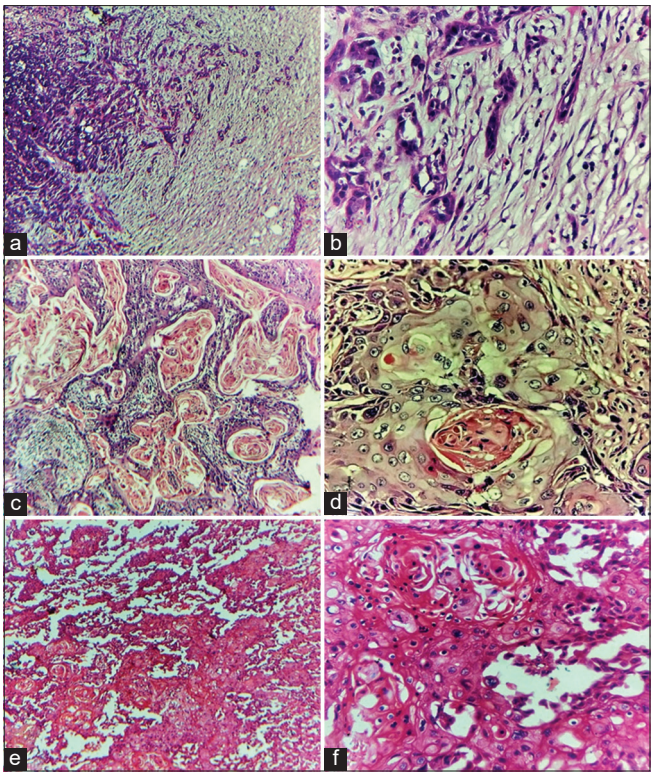

Figure 1: Pattern of invasion of cancer cells in cervical lymph nodes of oral squamous cell carcinoma. (a and b) The form of cords (H and E, ×100 and ×400); (c and d) in the form of island (H and E, ×100 and ×400); (e and f) in the form of total replacement (H and E, ×100 and ×400)

Grading of lymph node invasion (as per Don *et al.*[20]).

- Grade 1 – Micro-metastasis,
- Grade 2 – <50% of lymph node involved with metastatic OSCC cells,
- Grade 3 – >50% of lymph node involved with metastatic OSCC cells, and
- Grade 4 – Extracapsular extension.

Immunohistochemistry (IHC)

All lymph nodes were immunohistochemically stained by monoclonal rabbit α-SMA antibody (PR003, PathnSitu, India). IHC was performed according to standard protocols. Paraffin-embedded sections were deparaffinized in xylene twice for 5 min and hydrated in ethanol with a gradual concentration of 100%, 95%, and 70% for 3 min each. Slides were rinsed in distilled water. Antigen retrieval was performed using retrieval solution (PathnSitu pH 9 at 100 1C for 20 min) followed by cooling to room temperature for 1 h and washed 2 times with 0.1% phosphate buffered saline tween (PBST) for 3 min each. Slides were blocked at room temperature for 10 min using 0.3% H2O2 prepared with 1 × PBS. Slides were next incubated at room temperature for 30–40 min with α-SMA antibody (PathnSitu, India, Product code- PR003, 1:100). The secondary antibody used was HRP-conjugated

and was revealed by DAB (PathnSitu, India, Product code-OSH001). Serial sections obtained from non-metastatic lymph nodes were stained by CK 5/6 cocktail antibody (PathnSitu, India, Product code- PR106) following standard method. Images were obtained using a trinocular microscope (Lawrence and Mayo, equipped with a camera of 5 MP). Images were captured at ×400 magnification for evaluation.

Quantification of α-SMA IHC

As per the standard protocol of scoring, 10 random high-power fields were selected each for all samples (×400; Lawrence and Mayo, India) and analyzed independently by two observers. The following intensity scores (IS) were attributed according to degree of staining: Score 0, absence of staining; score 1, weak staining; score 2, moderate staining; and score 3, strong staining. The proportion score (PS) was attributed as per the percentage of stained cells (0, 0–5%; 1, 5–25%; 2, 25–50%; and 3, >50%). Multiplication of the intensity score (0–3) and proportion score (0–3) gives the overall staining intensity in a range 0–9. Average of scores of 10 fields was considered as the final staining score of the sample. The immunoreactivity was divided into three groups on the basis of final score.

Total score:

- <3 = Low positive
- 3–6 = Positive
- 6 ≥ = High positive

Statistical Analysis

The data were compiled and statistically analyzed using SPPS software version 21.0 (SPSS, Inc. IBM, USA). A comparison of α-SMA expression with various clinicopathological parameters such as age, gender, stage of primary tumors, POI in lymph nodes, and invasion grades of metastatic lymph nodes was done by the Chi-square test. ANOVA was employed to compare α-SMA expression with tumor differentiation and sites of primary tumor. Kappa statistics was performed to detect interobserver variability. *P* value of 0.05 or less was considered to be statistically significant.

RESULTS

Immunohistochemical Expression of α-SMA Positive Myofibroblasts in Metastatic Lymph Nodes

All metastatic lymph nodes (N = 50) showed positive expression of myofibroblast identified by α-SMA antibody in contrast to lack of expression in the body of non-metastatic lymph nodes (N = 10). The capsule of all lymph nodes showed a positive expression.

Expression of α-SMA Positive Myofibroblasts in the POI in Lymph Nodes

Higher expression of myofibroblast was detected in total replacement followed by cords and islands. Chi-square test revealed a highly significant difference in α-SMA expression in different lymph node invasion patterns ($p < 0.001$) [Table 1 and Figure 2a].

Expression of the Myofibroblasts in Different Grades of Lymph Nodes Invasion

A significant difference ($p < 0.001$) in the expression of the myofibroblasts in the different grades of lymph nodes invasion was noted. Grade 4 invasion cases showed more high positive expression than in Grade 2, where the high positive scores were the lowest [Table 1 and Figure 2b].

Distribution Pattern of the Myofibroblast in Metastatic Lymph Nodes

Three different patterns of myofibroblast distribution in metastatic lymph nodes were observed- focal, spindle, and network [Figure 3b-d]. Predominant network (36%) along with an equal percentage of focal and spindle (32%) patterns were observed. Statistically no significant

Table 1: Comparison of myofibroblasts expression with various pathological parameters of OSCC (χ^2)

Variables	Myofibroblasts expression			χ^2	*P*
	Low positive, *n* (%)	Positive, *n* (%)	High positive, *n* (%)		
POI					
Island	11 (61.1)	10 (55.6)	1 (7.1)	28.666	0.001*
Cords	6 (33.3)	0	4 (22.2)		
Total replacement	1 (5.6)	4 (22.2)	13 (92.9)		
Lymph node invasion grade					
Grade II	15 (83.3)	5 (27.8)	1 (7.1)	34.659	0.001*
Grade III	3 (16.7)	12 (66.7)	5 (35.7)		
Grade IV	0	1 (5.6)	8 (57.1)		
Pattern of myofibroblast					
Focal	5 (27.8)	5 (27.8)	6 (42.9)	5.693	0.223
Spindle	8 (44.4)	7 (38.9)	1 (7.1)		
Network	5 (27.7)	6 (33.33)	7 (38.88)		

* p=.001 is significant

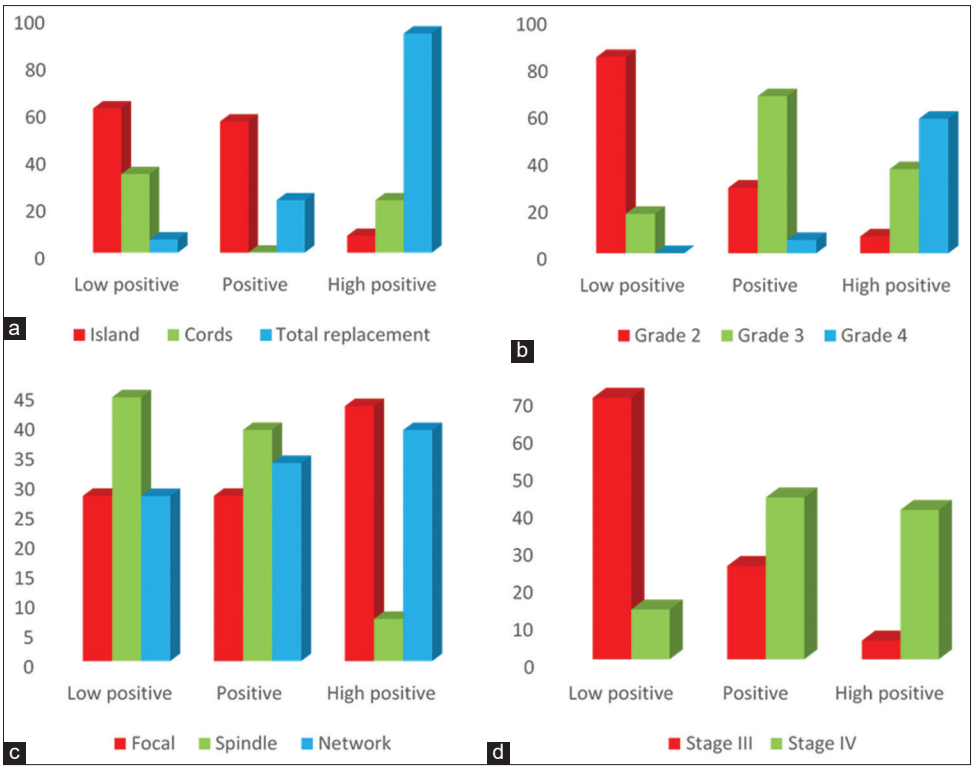

Figure 2: (a) Comparison of myofibroblasts expression in different pattern of invasion in lymph nodes revealing highest expression in total replacement; (b) comparison of myofibroblasts expression with grades of invasion in lymph nodes showing more high positive expression in grade IV cases; (c) comparison of pattern of myofibroblasts; and (d) comparison of myofibroblasts with tumor stage showing Stage IV tumor expressing more high positive and positive expression than Stage III tumor

difference of α-SMA expression in different distribution patterns ($P = 0.223$) was noted [Table 1 and Figure 2c].

The expression of myofibroblast was compared with different parameters like the age, gender, site, size and tumor differentiation which did not show significant differences [Tables 2 and 3]. A significant difference was noted in Stage IV cases than in Stage III cases ($p < 0.001$).

DISCUSSION

One of the key critical events in metastasis is pre-metastatic conditioning of lymph node micro-environment. However, there is a lack of extensive work investigating the participation of stromal cells in the induction of tumor microenvironment in cervical lymph nodes. To the best of our knowledge, the present study is only one of the few to report presence of myofibroblasts in cervical lymph nodes containing OSCC metastases and perhaps the first to compare its expression with the POI and grade of lymph node invasion.

In the present study, it is broadly observed that myofibroblasts, as identified by α-SMA positivity, occur abundantly within body of lymph nodes in agreement with Vered *et al.*[21] study containing OSCC metastases. This is in complete contrast to uninvolved lymph nodes of OSCC cases, where no internal myofibroblasts are seen (Figure 3a). Hence, it can be strongly assumed that the activation and recruitment of the myofibroblasts are brought about by the metastatic cancer cells into the lymph nodes. Cancer cells induce a favorable microenvironment that supports their existence and growth in lymph nodes similar to the primary tumor. The capsule in normal lymph node contains myofibroblasts, but the internal structure is devoid of such cells, the activation of which in metastatic lymph nodes is not a passive reaction.[18,21] A plausible explanation is that the capsular myofibroblasts provide specific attachment or anchorage point to the infiltrating cancer cells, thus helping them to establish themselves in the lymph nodes.[18] It is presumed that the capsule is a source of the activated myofibroblasts encountered in lymph node metastases of colorectal carcinoma.[18] Other sources of activated myofibroblasts like bone marrow is also hypothesized.[22]

Myofibroblast expression was, further, corelated with different patterns of lymph node invasion determined as island, cords, and total replacement types. The predominant pattern was found to be islands which is in agreement with previous study.[19] Highest expression of myofibroblast was observed (92% high positive) in total replacement

Table 2: Comparison of myofibroblasts expression with various clinical parameters of OSCC (χ^2)

Variables	Myofibroblasts expression			χ^2	*P*
	Low positive, *n* (%)	Positive, *n* (%)	High positive, *n* (%)		
Age					
<50 years	5 (33.33)	4 (26.66)	6 (40)	3.154	0.432
≥50 years	11 (31.42)	9 (25.71)	15 (42.85)		
Gender					
Male	13 (37.1)	11 (31.4)	11 (31.4)	4.637	0.327
Female	5 (35.7)	7 (50)	2 (14.3)		
Tumor size					
<5 cm	15 (38.46)	15 (38.46)	9 (23)	2.131	0.345
≥5 cm	3 (16.7)	3 (16.7)	5 (35.7)		
Tumor stage					
Stage III	14 (70)	5 (25)	1 (5)	18.122	0.001*
Stage IV	4 (13.33)	13 (43.33)	12 (40)		

OSCC: Oral squamous cell carcinoma; p=.001 is significant

Table 3: Comparison of tumor differentiation and intra oral sites of primary tumor with myofibroblasts expression in lymph nodes of OSCC (ANOVA)

Source of variation	Sum of squares	Df	Mean square	*F*	*P*
Tumor differentiation					
Between groups	1012.140	5	202.428	0.885	0.499
Within groups	10063.860	44	228.724		
Intraoral tumor site					
Between groups	0.118	3	0.070	0.125	0.779
Within groups	26.90	44	0.473		

OSCC: Oral squamous cell carcinoma

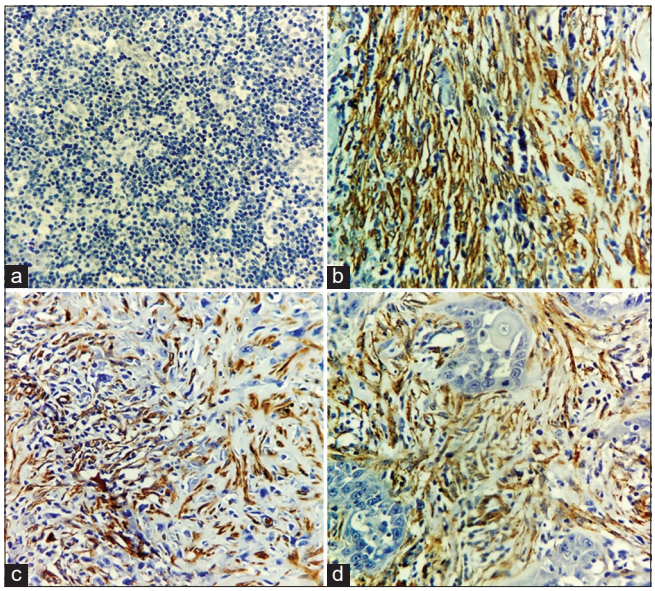

Figure 3: (a) Non-metastatic lymph node showing no expression of α-SMA positive myofibroblasts and (b-d) metastatic lymph nodes showing network, focal, and spindle arrangement of myofibroblasts (immunohistochemistry, ×400)

followed by cords (22.2% high positive) and islands (7.1% high positive) and these association was found to be highly significant ($P < 0.001$) [Table 1]. This study is the first to compare myofibroblast expression with POI in lymph nodes. The present study stated that an increased myofibroblasts might facilitate cancer cells in establishing and causing total effacement of lymph nodes. Further investigations are needed to confirm this fact.

An assessment of the distribution of grade of invasion in metastatic nodes was also made which revealed grade 2 invasion as predominant (42%), followed by grade 3 (40%) and grade 4 (18%). The expression of myofibroblast was highest in grade 4 (57.1% high positive), followed by grade 3 (35.7% high positive) and grade 2 (7.1% high positive) [Table 1]. A highly significant increase in myofibroblasts expression was noted with increasing lymph node grade ($p < 0.001$). That means myofibroblasts expression increases with the extent and volume of metastatic OSCC cells in lymph nodes. Yeung *et al.*[18] observed an increase in myofibroblasts expression in metastatic lymph nodes of colorectal carcinoma and it significantly correlated with the size of the metastasis. The increased expression of myofibroblasts with lymph node grading warrants that the metastatic OSCC cells are still dependent on their microenvironment. The association of myofibroblast expression in micrometastasis could not be investigated, because no micrometastasis was detected in lymph nodes under this study as ascertained by serial sectioning of negative lymph nodes and subsequent immunostaining with cytokeratin. It may be due to the inclusion of a small number of negative lymph nodes ($n = 10$).

On the evaluation of the distribution pattern of myofibroblasts, α-SMA expression was observed mostly between and around the neoplastic islands in lymph nodes. Myofibroblasts expression was also evident in the capsule of both metastatic and non-metastatic lymph nodes. A similar expression of myofibroblasts was found in the previous studies.[18,21] In this study, three different

patterns of myofibroblasts distribution in metastatic lymph nodes were observed – focal, spindle, and network (Figure 3b-d). Network pattern, predominated (36%) along with an equal percentage of focal, and spindle (32%) patterns were observed. A similar pattern of distribution of myofibroblasts was noted in the primary OSCC (Vered *et al.*[21], Alka *et al.*[23], and Smitha *et al.*[24]), but hitherto not explored in metastatic lymph nodes. A significant difference ($P = 0.223$) [Table 1 and Figure 2c] in myofibroblasts expression between these patterns has not been reached in the present study. Khalid *et al.*[25] showed that network pattern was more discerned often in poorly differentiated carcinomas. It is likely that neoplastic lesions show more invasive behavior and poorer prognosis due to the higher number of myofibroblasts arranged in network pattern.[26] The present study could not find such an observation and that might be due to a small number of PDSCC samples and a lack of follow-up data.

The expression of α-SMA positive myofibroblasts in various stages of the tumor was also compared. While all 50 metastatic lymph nodes were obtained from Stage III and Stage IV cases of OSCC, a significant difference in myofibroblast expression between Stage III and IV OSCC was observed ($P < 0.001$) [Table 2]. The above finding could be explained by the fact that Stage IV OSCC cases showed higher grade of lymph node invasion than Stage III cases [Figure 4] and myofibroblast expression increases with lymph node invasion grade. This could be one of the reasons for the higher expression of myofibroblasts in Stage IV cases.

However, the expression of myofibroblasts with other tumor related parameters such as the intraoral site, size, tumor differentiation, age, and gender of the patient was of no significance [Table 2].

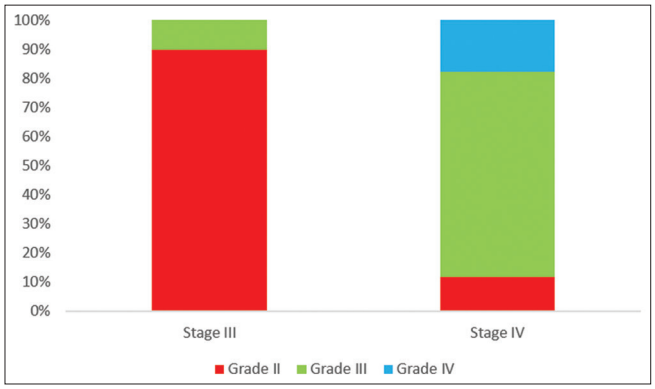

Figure 4: Percentage distribution of lymph node invasion grades in Stage III and Stage IV oral squamous cell carcinoma

CONCLUSION

The presence of activated myofibroblasts in lymph nodes and their increased expression with lymph node invasion grades and POI highlights the importance of the microenvironment in supporting cancers, even in the late metastatic stages. Further, understanding of the interaction between myofibroblasts and metastases may provide novel therapeutic targets for OSCC.

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Original Article

Evaluation of the Effect of Addition of Clonidine to 0.5% Ropivacaine in Supraclavicular Brachial Plexus Block

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Abstract

Background and Aims: The aim of the study was to evaluate the effect of addition of clonidine to 0.5% Ropivacaine in supraclavicular brachial plexus block (Ultrasound Guided) in terms of onset and duration of sensory motor blockade, post-operative analgesia, and intraoperative sedation score.

Methods: In this randomized, double-blind, and placebo-controlled study, supraclavicular brachial plexus block was performed in 60 patients divided into two groups – RC Group: Patient receiving 1 mL of Clonidine (150 μg) ± 35 mL of 0.5% Ropivacaine (175 mg), R Group: Patient receiving 1 mL of Normal saline ± 35 mL of 0.5% Ropivacaine (175 mg). Both groups were compared with the onset and duration of sensory motor blockade and post-operative analgesia.

Results: There was a significant decrease in onset time of sensory ($P = 0.007$) and motor blockade ($P = 0.05$) in RC Group which was statistically significant. There was a significant prolongation in the duration of sensory ($P < 0.001$), motor blockade ($P < 0.001$), and analgesia ($P < 0.001$) in RC Group which was statistically significant.

Conclusion: The addition of 150 μg clonidine to 0.5% Ropivacaine in supraclavicular brachial plexus block provides rapid onset and extends the duration of sensory motor blockade and post-operative analgesia.

Key words: Clonidine, Post-operative analgesia, Ropivacaine, Supraclavicular brachial plexus block, Ultrasound

INTRODUCTION

Supraclavicular brachial plexus is commonly practiced for upper limb surgeries. Ropivacaine[1] is an aminoamide local anesthetic prepared as pure S-enantiomer with lesser toxicity profile. Clonidine[2] is an α2 agonist that has been used as an additive to peripheral nerve blocks. Ultrasound-guided supraclavicular brachial plexus block has become popular due to reliable block and lesser complications.[3] The present study is a randomized, double-blinded, placebo, and control study to evaluate the effects of clonidine administration with Ropivacaine in supraclavicular brachial plexus block.

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METHODS

After getting approval from the Institutional Ethical Committee KAPV Medical College and Mahatma Gandhi Memorial Government Hospital, we performed the study from October 2021 to September 2021. Sixty patients aged between 18 and 60 years with ASA I and II scheduled for various elective surgeries lower arm, at the level of elbow, forearm, and hand were included in the study. Those with age <18 years and >60 years, on anticoagulant drugs, allergy to study drugs, history of peripheral neuropathy, history of brachial plexus injury, and infection at the site of injection were excluded from the study.

Patients were randomly allocated into two groups by computer generation table, Group RC: ($n = 30$) received 175 mg of 0.5% of Ropivacaine (35 mL) ± 150 μg (1 mL) of Clonidine (36 mL) and Group R: ($n = 30$) received 175 mg of 0.5% of Ropivacaine (35 mL) ± 1 mL of Normal saline (36 mL).

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To ensure blinding, the study drug solutions were prepared by another assistant professor who was not involved in the study. In the preparation room, anesthetic procedure and visual analogue scale (VAS) score was thoroughly explained to the patients. After getting informed consent, patient shifted to operation theater. Intravenous access secured by 18 G I.V cannula in the non-operating limb and Ringer lactate was started. After attaching standard monitors, baseline heart rate, blood pressure, and oxygen saturation were recorded. Under strict aseptic precautions, supraclavicular brachial plexus block performed by ultrasound-guided approach in plane technique using 18G I.V. cannula needle after adequate local anesthetic skin infiltration. Time at the end of drug injection was taken as 0 min.

Assessment of sensory block in the cutaneous distribution of musculocutaneous, radial, median, and ulnar nerves was assessed every 3 min by pin pricking method using 24 G hypodermic needle.[4] The sensory block was graded as Grade 0: Sharp pin felt, Grade 1: Analgesia, dull sensation feltm and Grade 2: Analgesia, no sensation felt.

Motor blockade was assessed every 3 min by "3-point Modified Bromage Scale"[4] for upper limb as Grade 0: Normal motor function with full extension and flexion of elbow, wrist, and finger, Grade 1: Decrease motor strength with ability to move finger only, and Grade 2: Complete motor block with inability to move finger.

If any one or more of the nerve segments did not get blocked even after 30 min after drug injection, the block was considered incomplete or failed. These patients were either supplemented with rescue blocks or general anesthesia as appropriate and the surgery was completed and they were excluded from the study. Hemodynamic parameters such as blood pressure, heart rate, and oxygen saturation every 15 min during the surgery and every 60 min postoperatively were monitored. Patient's sedation score was assessed by Ramsay sedation score.[5] The sedation score was assessed every 5 min during the surgery till it reached maximum level whereas it was assessed every 30 min till the patient was fully awake in the post-operative period.

Post-operative pain was assessed as per visual analog score using word scale (VAS).[6] Score recorded every 60 min after the surgery (post-operative period) till the score reached 4. If the score reached 4, rescue analgesia was given in the form of Inj. Diclofenac 1.5 mg/kg i.m. All the patients were observed for any side effects such as dry mouth, nausea, vomiting, bradycardia, hypotension, and complication such as pneunothorax, local anesthesia toxicity, and hematoma at the site of injection.

The sensory block duration was defined from the time of injection of study drug solution to complete sensory [Table 1] recovery of all nerves whereas the motor block [Table 2] duration was defined as the time interval between the injection of study drug solution to complete recovery of motor function of hand and forearm. The primary outcome measures were the onset and duration of sensory motor block and duration of analgesia whereas the secondary outcomes were the sedation score and occurrence of any side effects and complications.

Statistical Analysis

Statistical analysis was done with SPSS 16 version. Qualitative data were analyzed by Chi-square test. Quantitative data such as time of onset of sensory and motor blockade, duration of sensory and motor blockade, and a duration of analgesia were expressed as mean ± SD. These data were analyzed by unpaired Student's "t"-test.

RESULTS

Demographic characteristics such as age, sex, weight, and ASA status were comparable among the two groups. There was no statistically significant difference noted between these demographics [Chart 1].

The mean onset time of sensory block in Group RC was 5.8 ± 2.72 when compared with 7.70 ± 2.53 min in Group R that was statistically significant ($P = 0.007$).

The motor block onset was 9.03 ± 2.72 min and 10.63 ± 2.785 min in Group RC and R, respectively, with $P = 0.05$. The mean duration of sensory block in Group RC and Group R were 534.67 ± 62.449 and Group R 441.50 ± 41.004 min, respectively, ($P < 0.001$). The mean duration of motor block in Group RC was 498.00 ± 53.233 min and in Group R was 400.67 ± 38.200 min ($P < 0.001$).

The duration of analgesia was significantly prolonged in RC group (656.7 ± 86.256 min) than R group (502 ± 53.169 min), which was also statistically highly significant ($P < 0.001$) [Figure 1].

The pain score was observed at the end of surgery. At 2 h, the mean VAS score in both groups was zero. After 8 h, the mean VAS score in RC group which was not statistically significant. Sedation score of patients was maximum at 30 min in RC group 2.37 ± 0.669 and in R group 1.70 ± 0.466. Thereafter, the sedation score was decreased. The statistical analysis showed significant difference. In RC group, 10 patients had dry mouth. None of the patient had headache, nausea, or vomiting. Incidence of dry mouth was 16.4% in RC group which was highly significant. In R group, only three patients had headache (4.9%), nausea

and vomiting noted in one patient only (1.6%) that was not statistically significant.

DISCUSSION

In our study, supraclavicular brachial plexus block was performed under ultrasound guidance. All the patients had successful brachial plexus block and hence satisfactory surgical anesthesia. We observed that 150 μg of Clonidine added to 175 mg of 0.5% Ropivacaine, resulted in excellent quality of supraclavicular brachial plexus block for upper limb surgeries. The advantage of Clonidine added as an adjuvant to Ropivacaine was rapid onset and prolonged duration of sensory and motor blockade and the duration of post-operative analgesia.

We observed that onset time of sensory blockade was significantly decreased in RC group when compared to R group. The mean onset time of sensory blockade in RC group was (5.8 ± 2.72) min and in R group (7.7 ± 2.5) min. Routary *et al*.[7] showed the mean onset time of sensory blockade in their study group was 10.44 ± 5.7 min and in control group was 15.85 ± 6.55 min. The delayed onset of sensory block in the study by Routary *et al.* in spite of adding clonidine would have been due to the landmark technique used in administering the block. In our study, we administered the block under ultrasound guidance which has helped in deposition of the local anesthetic in close proximity to the plexus contributing to the early onset of the sensory block.

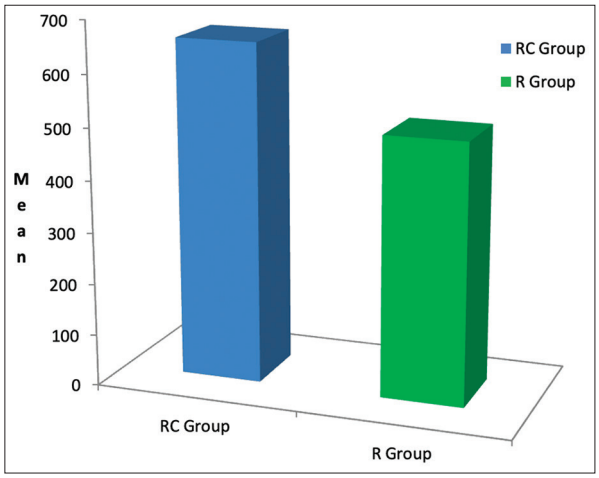

Figure 1: Duration of analgesia

The mean onset time of motor blockade in RC group was (9.3 ± 2.72) min. as compared to R group (10.63 ± 2.785) min which was statistically significant. Ali *et al*.[8] showed the mean onset time of motor blockade in study group (Ropivacaine 0.5% ± 75 mcg clonidine) was 13 ± 3.69 min and in control group was 15.05 ± 4.21 min.[6] The reason for early onset of motor blockade in our study would have been due to accuracy of needle placements close to the plexus, higher volume of local anesthetic (35 mL instead of 30 mL) and higher dose of clonidine (150 μg instead of 75 μg).

The mean duration of sensory blockade in RC group was (534.67 ± 62.449) as compared with R group (441.50 ± 41.004) min. The mean duration of motor blockade in RC was (498.00 ± 53.233) min, compared with R group (400.67 ± 38.200) min. Prolongation of sensory and motor blockade was in RC group was statistically significant. Our observation concur with those obtained by Ali *et al.*

The duration of motor block was less than the sensory block due to increased requirement of local anesthetic for larger motor fiber than small sensory fiber. Gupta *et al*.[9] have shown earlier onset of sensory and motor blockade and prolonged duration of sensory and motor

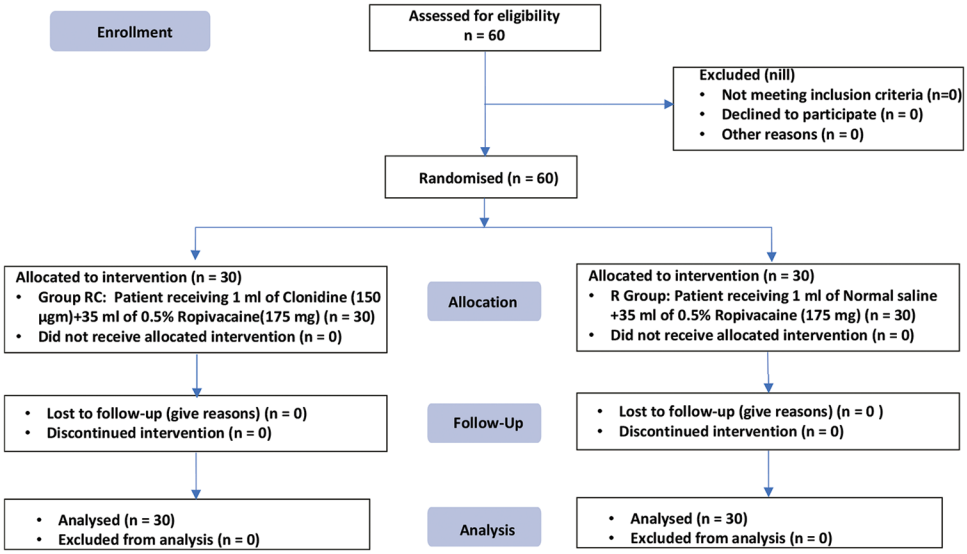

Chart 1: Consort flow chart

Table 1: Demographic profile between RC and R group

Demographic profile	Group RC	Group R	*P*-value
Sex (Male: Female)	18:12	20:10	0.437
Mean age (years)	36.77±11.913	39.20±12.169	0.599
Mean weight (kg)	59.33±9.245	55.47±8.244	0.068
ASA status (%) 1:2	48.2%: 75.00%	51.8: 25.00%	0.301

Table 2: Onset and duration of sensory and motor block

Onset time and duration of sensory and motor block	Group RC	Group R	*P*-value
	Mean±SD		
Sensory block			
Onset (min)	5.8±2.72	7.70±2.53	0.007
Duration (min)	534.67±62.449	441.50±41.004	<0.001
Motor block			
Onset (min)	9.03±2.72	10.63±2.785	0.05
Duration (min)	498.00±53.233	400.67±38.200	<0.001

blockade with ultrasound versus other nerve localization techniques. The combined administration of clonidine and ropivacaine local anesthetics (synergistic mechanism) results in prolonged effect of sensory and motor blockade.

Duration of analgesia was significantly prolonged in RC group than control R group which was statistically highly significant. Gupta *et al.* showed the duration of analgesia in study group was 956.47 ± 38 min and in control group was 736.53 ± 47 min. "Sia and Lepri"[10] observed the synergistic mechanism between clonidine and ropivacaine. The mechanism of action of Clonidine to enhance the peripheral nerve block by "Vasoconstriction theory"[11] $\alpha 2$ Adrenergic stimulation causes decreased systemic absorption of local anesthetics (Ropivacaine) and Ropivacaine has an intrinsic vasoconstriction effect. This intrinsic vasoconstriction effect of Ropivacaine is not enhanced by Epinephrine. Clonidine has direct-action on A delta and C fibers and inhibits the nerve conduction, which further augments conduction block of local anesthetics.

VAS score in post-operative period up to 6 h was comparable in both groups. RC group reached maximum VAS score at 10 h and R group at 8 h, showing extended duration of analgesia in RC group. Ali *et al* also has similar results.

Sedation score was measured as per Ramsay sedation scale. Maximum sedation level in RC group means score was 2.37 at 30 min as compared with 1.63 at 45 min in R group. Our observation concurs with those obtained by Gupta *et al.* None of the patients had significant bradycardia and hypotension. Our observation concurs with those obtained by Routary *et al.* Dry mouth was observed in Clonidine group (16%) whereas it was nil in Ropivacaine group. Nausea, vomiting, and headache was present only in R group. Similar results were obtained by other investigators. No other complications were present in both the groups.

The limitations of our study were small sample size and drugs (Clonidine and Ropivacaine) were not calculated as per body weight. All the patients irrespective of body weight received the same dose of Ropivacaine and Clonidine. However, body weight was comparable in both two groups.

CONCLUSION

The addition of clonidine to 0.5% Ropivacaine in supraclavicular brachial plexus block in patients undergoing upper limb surgeries provided rapid onset as well as prolonging the duration of sensory and motor blockade. In addition, it extends the duration of analgesia with good hemodynamic stability with optimum sedation.

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Original Article

A Comparative Study of Intrathecal Tramadol versus Fentanyl as Adjuvant to Bupivacaine in Lower Abdominal and Lower Limb Surgeries

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Abstract

Aim: The study is aimed to compare the effect of intrathecal fentanyl- bupivacaine versus tramadol – bupivacaine on the onset and duration of sensory and motor blockade, as well as postoperative analgesia in lower abdominal surgeries and lower limb surgeries.

Methods: After obtaining approval from Institutional Ethical Committee and informed written consent, 60 patients of ASA physical class I and II who were posted for elective lower abdominal and lower limb surgeries were taken for the study. Group BF: Received 12.5 mg (2.5 mL) of 0.5% hyperbaric Bupivacaine with 25 μg of Fentanyl citrate intrathecally. Group BT: Received 12.5 mg (2.5 mL) of 0.5% hyperbaric Bupivacaine with 25 mg of tramadol intrathecally.

Results: Motor blockade and sensory blockade onset, maximum level of sensory blockade attained and time taken for the same, and motor blockade maximum level attained were taken.

Conclusion: Adding fentanyl or tramadol to bupivacaine induced similar hemodynamic alterations, post-operative analgesia, and sensory blockage without delaying motor recovery. Both the drugs showed equal potency in the study.

Key words: Bupivacaine, Fentanyl, Tramadol

INTRODUCTION

The common regional anesthetic procedures used for lower limb and lower abdominal surgeries are intrathecal and epidural anesthesia.

For lower abdominal procedures, spinal anesthesia is popular and widely utilized around the world. Spinal anesthesia has the advantage of requiring a small amount of anesthetic, being straightforward to administer, and providing a quick onset of effect, dependable operative analgesia, and adequate muscular relaxation. These benefits are sometimes outweighed by the fact that the action lasts just a short period and causes discomfort when it wears off.

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Because spinal anesthesia with only local anesthetics has a shorter duration of action, post-operative pain control is a serious issue. As a result, in the post-operative period, early analgesic management is essential. Nausea, visceral pain, and vomiting are common side effects of lower abdominal procedures performed under spinal anesthesia. A variety of adjuvants, including opioids (morphine, fentanyl, and tramadol) and non-opioids (dexmedetomidine, clonidine), as well as midazolam and steroids, have been explored to extend the effects of spinal anesthesia.

The lipophilic opioid fentanyl has a fast beginning of action. Fentanyl diffuses into the epidural region and then into the bloodstream after intrathecal administration, implying that it operates not just through spinal opioid receptors but also systemically. In comparison to intrathecal Bupivacaine alone, adding Fentanyl to hyperbaric Bupivacaine improves

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the quality of intraoperative and early post-operative subarachnoid block.

This study is designed to quantitatively examine the effects of adding fentanyl and tramadol to hyperbaric bupivacaine hydrochloride spinal anesthesia on duration and recovery of sensory and motor blockade.

Aim of the Study

The study is aimed to compare the effect of intrathecal fentanyl- bupivacaine versus tramadol – bupivacaine on the onset and duration of sensory and motor blockade, as well as post-operative analgesia in lower abdominal surgeries and lower limb surgeries.

Objectives of the Study

The objectives of the study are to compare

- Onset of sensory block
- Onset of motor block
- Sensory block duration
- Duration of motor block
- Intraoperative hemodynamic changes.

METHODS

Source of Data

After obtaining clinical approval from the Institutional Ethical Committee and informed written consent, 60 patients of ASA physical class I and II who were posted for elective lower abdominal and lower limb surgeries at GGH Vijayawada were selected for the study.

The present, prospective, randomized, double-blinded, and clinical study was conducted from December 2019 to June 2021.

- Group BF: Received 12.5 mg (2.5 mL) of 0.5% hyperbaric Bupivacaine with 25 μg of fentanyl citrate intrathecally
- Group BT: Received 12.5 mg (2.5 mL) of 0.5% hyperbaric Bupivacaine with 25 mg of tramadol intrathecally.

Inclusion Criteria

The following criteria were included in the study:

- 60 patients of ASA physical grades I and II
- Patients of either sex aged 18–60 years taken for lower abdominal and lower limb surgeries.

Exclusion Criteria

The following criteria were excluded from the study:

- Patient refusal
- Patient on adrenoreceptor agonists and antagonists
- Patient with cardiovascular comorbidities
- Patient allergic to study drugs
- Patient with ASA grade 3 and 4
- Patients with obesity.

Methods of Collection of Data

Data were collected from 60 patients in the age group of 18–60 years of ASA class I and II, taken for lower abdominal and lower limb surgeries without any comorbid diseases were grouped randomly. The study drug was prepared by an anesthesiologist, who was not included in the study. All spinal blocks were given by the same anesthesiologist, who was also an observer. Hence, the patient and the observer were blinded for the study drug.

- Pre-operative assessment done for each patient on the night before the surgery
- And written informed consent was taken
- Patients were kept Nil per Oral for solids 6 h and clear fluids 2 h before surgery
- Patients are pre-medicated on the night before surgery with the tablet Alprazolam 0.5 mg
- Patients were not pre-medicated on the day of surgery
- Intravenous line was secured with 18G cannula
- Patients were connected to a multi-channel monitor for continuous monitoring of pulse rate (PR), arterial oxygen saturation (SpO_2), electrocardiograph (ECG), non-invasive blood pressure, and mean arterial pressure (MAP)
- Patients were positioned in flexed lateral position
- Under aseptic precautions, subarachnoid blocks were performed at L2-L3/L3- L4 inter-space through a midline approach using 25G Quincke's spinal needle after confirming the clear and free flow of CSF and the study drug was injected into the subarachnoid space. Patients are turned to supine posture immediately with the table kept flat and supplemental O_2 was given.

The following parameters were recorded.

- Motor blockade and sensory blockade onset
- Maximum level of sensory blockade attained and time taken for the same
- Time taken for two segments sensory regression
- Motor blockade maximum level attained and time taken for the same
- Total duration of the sensory blockade and motor blockade
- Total duration of analgesia
- Using the pinprick method with a 27G hypodermicneedle sensory blockade is tested at every 30 s for the first 2 min, every minute for the next 5 min and every 5 min for the next 15 min, and every 10 min for the next 30 min and every 15 min till the end of surgery and thereafter every 30 min until the sensory block is reduced
- The motor blockade was assessed according to the Modified Bromage scale

- All of the patients monitored during the period of a block and perioperative period employing a multi-channel monitor which displays PR, systolic and diastolic blood pressure (DBP), MAP, ECG, and SpO_2
- Patients were followed for post-operative discomfort during the recovery period by VAS scale (0–10) initially every hour for 2 h, then every 2 h for the next 8 h, then every 4 h till 24 h, which was explained to the patients preoperatively. When the VAS was, >4 patients were given rescue analgesia with Inj. Diclofenac 75 mg intramuscularly.

RESULTS

The study population consists of 60 patients (20–50 years) posted for lower abdominal and lower limb surgeries. They were divided into two groups 30 in each group.

- Group-Fentanyl-received 0.5% hyperbaric Bupivcaine 12.5 mg (2.5 mL) + 25 μg Fentanyl
- Group-Tramadol -received 0.5% hyperbaric Bupivacaine 12.5 mg (2.5 mL) + 25 mg Tramadol.

The following observations were made during the study.

Distribution of Study Population According to Age [Table 1]

Both groups were similar with respect to age distribution and there was no statistically significant difference between 2 groups(P=0.68) [Table 1].

Distribution of Study Population According to Anthropometric Parameters [Table 2]

There was no significant difference in the weight and height of the study subjects among two groups [Table 2].

Comparison of Heart Rate among Both the Groups [Table 3]

Significant difference is not present in HR measured at various intervals throughout the surgery among the groups(P>0.05) [Table 3].

Comparison of Systolic Blood Pressure (SBP) among Both the Groups [Table 4]

No statistically significant difference in SBP(mm of Hg) measured at different intervals throughout the surgery among the groups(P>0.05) [Table 4].

Comparison of DBP among Both the Groups [Table 5]

Statistically there was no significant difference in DBP measured at different intervals throughout the surgery among the groups(P>0.05) [Table 5].

Comparison of MAP among Both the Groups [Table 6]

Statistically there was no significant difference among the two groups in MAP (P>0.05) [Table 6].

Table 1: Age distribution

Age in mean	Mean±SD	*P*-value
Fentanyl	40.73±5.41	0.68
Tramadol	40.13±5.81	

Both groups were similar with respect to age distribution and there was no statistically significant difference between 2 groups (*P*=0.68)

Table 2: Weight and height distribution in both the groups

Parameter	Fentanyl Mean±SD	Tramadol Mean±SD	*P*-value
Weight (kg)	57.17±3.47	55.87±5.2	0.25
Height (cm)	158.27±4.63	160.83±5.42	0.26

There was no significant difference in the weight and height of the study subjects among two groups

Table 3: Mean HR (Bpm) at various intervals in min

Heart rate	Fentanyl		Tramadol		*P*-value
	Mean	SD	Mean	SD	
Basal	82.23	4.03	81.07	6.02	0.38
0 min	79.20	4.30	78.43	5.31	0.54
5 min	73.90	6.84	76.47	5.92	0.12
10 min	74.10	6.64	74.17	6.79	0.96
15 min	74.43	6.91	72.77	10.49	0.47
30 min	74.80	6.89	73.10	11.42	0.48
45 min	75.13	6.54	71.83	8.15	0.08
60 min	75.47	6.98	72.73	7.83	0.15
75 min	75.37	6.45	72.43	7.91	0.12

Significant difference is not present in HR measured at various intervals throughout the surgery among the groups (*P*>0.05), HR: Heart rate

Table 4: Mean SBP at different intervals in minutes

SBP	Fentanyl		Tramadol		*P*-value
	Mean	SD	Mean	SD	
Basal	126.03	5.35	125.33	5.67	0.62
0 min	122.23	4.85	121.67	4.75	0.60
5 min	116.07	4.24	115.27	5.34	0.52
10 min	118.70	6.26	116.00	7.40	0.611
15 min	118.30	4.35	117.0	17.70	0.69
30 min	118.17	4.04	116.47	4.71	0.13
45 min	118.20	3.30	116.87	3.91	0.15
60 min	118.40	4.44	117.73	4.11	0.54
75 min	117.90	4.35	118.93	3.83	0.33

No statistically significant difference in SBP (mm of Hg) measured at different intervals throughout the surgery among the groups (*P*>0.05), SBP: Systolic blood pressure

Comparison of SPO_2 among Both the Groups [Table 7]

Statistically significant difference is not seen among the two groups (P>0.05) [Table 7].

Comparison of Respiratory Rate among Both the Groups [Table 8]

Statistically there is no significant difference in both the groups (P>0.05) [Table 8].

Table 5: Mean DBP (mm of Hg) at various intervals in minutes

DBP	Fentanyl		Tramadol		*P*-value
	Mean	SD	Mean	SD	
Basal	80.50	3.22	80.63	3.26	0.87
0 Min	78.33	4.05	78.47	4.01	0.89
5 min	73.13	3.14	74.20	4.42	0.28
10 min	72.40	4.08	70.77	5.63	0.29
15 min	72.40	4.59	71.50	5.29	0.48
30 min	73.13	5.00	71.27	3.61	0.10
45 min	72.97	5.01	71.33	4.72	0.19
60 min	74.33	5.55	73.13	4.23	0.35
75 min	75.33	5.55	74.13	4.23	0.35

Statistically there was no significant difference in DBP measured at different intervals throughout the surgery among the groups (*P*>0.05), DBP: Diastolic blood pressure

Table 6: MAP (mm of Hg) at various intervals in minutes

MAP at various intervals in minutes	Fentanyl		Tramadol		*P*-value
	Mean	SD	Mean	SD	
Basal	95.53	3.17	95.73	3.09	0.80
0 min	92.80	3.34	92.93	3.44	0.80
5 min	87.83	3.62	86.17	2.71	0.04
10 min	85.23	5.75	87.87	4.85	0.07
15 min	85.57	4.54	87.70	4.69	0.07
30 min	85.33	3.28	86.13	3.75	0.38
45 min	88.23	3.93	89.43	3.68	0.22
60 min	88.33	4.56	89.63	4.24	0.25
75 min	89.93	4.59	90.07	4.19	0.90

Statistically there was no significant difference among the two groups in MAP (*P*>0.05), MAP: Mean arterial pressure

Table 7: Oxygen saturation at various intervals In minutes

SPO_2	Fentanyl		Tramadol		*P*-value
	Mean	SD	Mean	SD	
Basal	99.27	0.52	99.27	0.45	1.00
0 min	99.17	0.53	99.17	0.46	1.00
5 min	99.07	0.37	99.07	0.37	1.00
10 min	99.07	0.37	99.03	0.32	0.70
15 min	99.17	0.38	99.17	0.38	1.00
30 min	99.07	0.37	99.07	0.37	1.00
45 min	99.07	0.52	99.04	0.33	0.79
60 min	99.03	0.41	99.14	0.45	0.33
75 min	99.03	0.41	99.14	0.45	0.33

Statistically significant difference is not seen among the two groups (*P*>0.05)

Comparison of Sedation Score among Both the Groups [Table 9]

There is no significant difference statistically (P>0.05) [Table 9].

Comparison of Total Surgery Duration among Both the Groups [Table 10]

The mean duration of surgery does not show statistically significant difference among the two groups(P>0.05)[Table 10].

Table 8: Comparison of respiratory rate in min

Respiratory rate	Fentanyl		Tramadol		*P*-value
Basal	14.07	0.94	14.21	0.79	0.52
0 min	14.03	0.85	14.07	0.77	0.85
5 min	13.97	0.56	14.07	0.47	0.44
10 min	13.87	0.68	13.96	0.43	0.52
15 min	14.13	0.82	13.93	0.47	0.25
30 min	14.13	0.51	14.00	0.27	0.22
45 min	14.03	0.41	13.89	0.42	0.20
60 min	14.00	0.53	14.04	0.58	0.80
75 min	14.00	0.45	13.86	0.45	0.23

Statistically there is no significant difference in both the groups (*P*>0.05)

Table 9: Mean sedation score

Parameter	Group	Mean	SD	*P*-value
Sedation score	Fentanyl	1.97	0.41	0.28
	Tramadol	1.86	0.35	

There is no significant difference statistically (*P*>0.05)

Table 10: Mean duration of surgery in minutes

Parameter	Group	Mean	SD	*P*-value
Duration of surgery in min	Fentanyl	74.50	10.21	0.37
	Tramadol	72.14	10.09	

The mean duration of surgery does not show statistically significant difference among the two groups (*P*>0.05)

Table 11: Mean time taken for sensory onset in minutes

Sensory characteristics	Group	Mean	SD	*P*-value
sensory block onset time (min)	Fentanyl	1.23	0.39	0.15
	Tramadol	1.37	0.36	

Table 12: Time taken for maximum sensory blockade in minutes

Sensory characteristics	Group	Mean	SD	*P*-value
Max sensory level onset time (min)	Fentanyl	10.64	1.85	0.06
	Tramadol	11.46	1.47	

Statistically significant difference is not seen when both groups are compared (*P*>0.05)

Comparison of Sensory Characteristics among Both the Groups

The mean time of onset of sensory blockade at T 10 in Group-fentanyl was 1.23±0.39 mins and Group-tramadol was 1.37±0.36mins. Statistically significant difference is not seen among both the groups (*P* > 0.05) [Table 11].

Comparison of Maximum Sensory Blockade [Table 12]

Statistically significant difference is not seen when both groups are compared(P>0.05) [Table 12].

Mean Time for Regression of Sensory Block [Table 13]

Statistically significant differencewas not seen among the two groups (P>0.05) [Table 13].

Table 13: Mean time for regression of sensory block by two segments in minutes

Sensory characteristics	Group	Mean	SD	*P*-value
2 segment sensory regression (min)	Fentanyl	105.73	8.33	0.16
	Tramadol	102.64	8.32	

Statistically significant difference was not seen among the two groups (*P*>0.05)

Table 14: Mean duration of sensory regression to S1 in minutes

Sensory characteristics	Group	Mean	SD	*P*-value
Sensory regression to S1 (min)	Fentanyl	227.80	18.08	0.44
	Tramadol	224.57	13.60	

Statistically significant difference was not seen in both the groups

Table 15: Mean duration of analgesia at different intervals in minutes

Sensory characteristics	Group	Mean	SD	*P*-value
Total duration of analgesia (min)	Fentanyl	193.87	10.19	0.06
	Tramadol	188.61	9.87	

In both groups significant difference is not present statistically

Table 16: Mean time taken for motor block onset in minutes

Motor characteristics	Group	Mean	SD	*P*-value
Motor block onset time (min)	Fentanyl	1.07	0.25	0.59
	Tramadol	1.11	0.31	

Significant difference is not seen statistically in either groups

Table 17: Mean time taken for maximum motor blockade in minutes

Motor characteristics	Group	Mean	SD	*P*-value
Time taken for max motor blockade (min)	Fentanyl	10.33	0.76	0.34
	Tramadol	10.14	0.76	

Significant difference is not seen statistically in either groups

Table 18: Mean duration of motor blockade in minutes

Motor characteristics	Group	Mean	SD	*P*-value
Total duration of motor block (min)	Fentanyl	207.00	11.00	0.77
	Tramadol	206.29	8.39	

Significant difference is not seen statistically in both groups

Mean Duration of Sensory Regression to S1 in Minutes [Table 14]

Statistically significant difference was not seen in both the groups [Table 14].

Mean Duration of Analgesia at Different Intervals in Minutes [Table 15]

In both groups significant difference is not present statistically [Table 15].

Table 19: Maximum level of sensory block attained

Max sensory level attained	Group (No. of patients)		Total	*P*-value
	Fentanyl	Tramadol		
Level T4	26 86.0%	25 83.0%	51 85.0%	0.317
Level T6	4 14.0%	5 17.0%	9 15.0%	
Total	30 100.0%	30 100.0%	60 100.0%	

No significant difference is seen among both groups

Table 20: Comparison of bradycardia

Bradycardia	Group		Total	*P*-value
	Fentanyl	Tramadol		
No	26 89.0%	27 90.0%	53 86.0%	0.565
Yes	4 11.0%	3 10.0%	7 14.0%	
Total	30 100.0%	30 100.0%	60 100.0%	

No significant difference in bradycardia is seen among both groups

Table 21: Comparison of hypotension

Hypotension	Group		Total	*P*-value
	Fentanyl	Tramadol		
No	19 63.0%	23 76.0%	42 70.0%	0.22
Yes	11 37.0%	7 24.0%	18 30.0%	
Total	30 100.0%	30 100.0%	60 100.0%	

No significant difference in incidence of hypotension is seen among both groups

Table 22: Comparison of vomiting

Vomiting	Group		Total	*P*-value
	Fentanyl	Tramadol		
No	30 100.0%	28 86.7%	58 93.3%	0.117
Yes	0 0.0%	2 6.7%	2 3.3%	
Total	30 100.0%	30 100.0%	60 100.0%	

No significant difference in incidence of vomiting is seen among both groups

Comparison of Motor Characteristics among Both the Groups [Table 16]

Significant difference is not seen statistically in either groups [Table 16].

Mean Time Taken for Maximum Motor Blockade in Minutes [Table 17]

Significant difference is not seen statistically in either groups [Table 17].

Mean Duration of Motor Blockade in Minutes [Table 18]

Significant difference is not seen statistically in both groups [Table 18].

Comparison of Maximum Sensory Level among Both the Groups [Table 19]

No significant difference is seen among both groups [Table 19].

Comparison of Adverse Effects among Both the Groups [Tables 20-22]

In this study, there was no statistically significant difference in the adverse effects throughout the procedure. Patients who developed hypotension are managed by inj. Mephenteramine 6 mg I.V in incremental doses. In patients who developed bradycardia were managed by inj. Atropine 0.6 mg I.V. Patients who developed vomiting were managed by inj Ondansetron 4 mg I.V.

DISCUSSION

Effective pain management is critical for providing the best possible care to patients in the post-operative period. Despite breakthroughs in our understanding of pain biology, analgesic pharmacology, and the creation of more efficient treatments, patients continue to feel significant pain following surgery. If a method of analgesia is to be successful and widely available, it must be appropriate for use in a general surgical ward and require just simple routine nurse monitoring.

The medications lidocaine and bupivacaine are routinely used for spinal subarchnoid block. One downside of spinal anaesthesia using local anesthetics is only that analgesia disappears when the block is retracted, meaning a requirement for analgesics soon after surgery. In addition to producing discomfort, post-operative pain has other harmful consequences, particularly on the cardiorespiratory system.

Intrathecal opioids have been increasingly popular in recent years, but at the consequence of an increased risk of respiratory depression. Tramadol, on the other hand, is a centrally acting analgesic with little respiratory depressive effects due to its 6000-fold lower receptor affinity than morphine.

Although epidural tramadol has been found to provide adequate post-operative analgesia in patients undergoing major abdominal surgery or caesarian sections, its efficacy following intrathecal injection has not been adequately explored. As a result, we thought comparing the effects of intrathecally administered tramadol to those of fentanyl, a regularly used intrathecally administered opioid, might be informative.

Following intrathecal injections, fentanyl has a quick start and a short duration of action. It extends the time that bupivacaine causes sensory blockage. As described in an animal study by Wang *et al*.,[1] this shows a potential synergism between fentanyl and bupivacaine. Fentanyl is one among the safest opioids, Because most orthopedic procedures may be performed under spinal anesthetic, orthopedic patients were chosen.

Changes in cardiovascular and respiratory parameters during surgery:

Both groups saw a significant decline in blood pressure during the first 30 min of the experiment, but there was no significant difference in the pattern of decrease in systolic or DBP during this time. According to other studies, neuraxial opioids reduce sympathetic outflow and adding fentanyl to spinal analgesia increases the risk of hypotension after epidural blocking. Wang *et al*.[2] discovered that bupivacaine, not the intrathecal opioid employed, is responsible for the decrease in sympathetic efferent activity after spinal anesthesia. The action of 3 mL of bupivacaine, rather than the modest intrathecal opioid dosage, is most likely responsible for the significant reduction in blood pressure reported in this trial.

In 2003, Alhashemi and Kaki[3] discovered that intrathecal tramadol had no impact on the intraoperative hemodynamic profile.

In our investigation, no one in the study group had respiratory depression. The mean PaO_2 values in the epidurally injected tramadol group did not alter, according to Baraka *et al*.[4] in 1993. Yaddanapudi *et al*.[5] observed similar results with epidurally given tramadol in 2000.

The fentanyl group experienced 562.0 min of analgesia, while Group B experienced 551 min. When compared to utilizing a local anesthetic alone, this is a significantly longer period of analgesia. The mean duration of analgesia or the total dose of analgesics required in 24 h did not differ substantially between the two groups. In 2000, Jain and Sarasawat[6] discovered that intrathecal tramadol 25 mg combined with bupivacaine offered an average of 8 h of post-operative pain relief, which is similar to our finding. Tramadol given epidurally gave good post-operative pain management, according to Prosser *et al*.[7] in 1997, and Delilkan and Vijayan[8] in 1993.

The time taken for two-segment regression in sensory level did not show significant difference between two groups, according to our findings. In two groups, the two-segment regression of sensory level took an average time of 90 min. Other investigations found that when a local anesthetic was given alone, it took less time for two segment regression and Singh *et al*.[9] in 1995, Goel *et al*.[10] reported that intrathecal fentanyl amplifies and prolongs sensory anesthesia in their research.

In terms of intrathecal opioid side effects, patients in both groups experienced minor adverse effects. Only two patients in both groups experienced minor side effects. Pruritis was found in only two patients in both groups. The occurrence of mild pruritis and nausea in our study could be explained by the prophylactic use of ondansetion in both groups.

CONCLUSION

- Adding both opioids to the mix resulted in little intraoperative and post-operative complications
- Adding fentanyl or tramadol to bupivacaine induced similar hemodynamic alterations, post- operative analgesia, and sensory blockage without delaying motor recovery
- Both the drugs show equal potency in the study.

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Original Article

A Study of Neurocognitive Functioning in Euthymic Bipolar Patients with and without Alcohol Dependence

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Abstract

Introduction: Bipolar disorders are a large group of psychiatric disorders with signs and symptoms of pathological emotional disturbances.

Aim: The study aims to assess neurocognitive functioning in remitted bipolar individuals with and without a history of alcohol dependence and an average population.

Methods: A comparative study was conducted at the Institute of Mental Health Hospital Chennai. Informed consent was obtained from 99 patients after a proper explanation of the purpose and procedure of the study. A selection of two groups of patients with bipolar affective disorder, of which one group is with alcohol dependence, while the other is without prior history of alcohol dependence.

Results: The mean age of subjects in the cases Group A is 32.2 years. The mean age of subjects in cases Group B is 33.5 years. The mean age of subjects in control is 33.8 years. In addition, the duration of illness of bipolar disorder significantly negatively correlated with performance on measures of perseverative error and total error of executive function and Hits 1 and 2 of N Back test of bipolar subjects with alcohol non-dependent. In alcohol dependent group, the number of episodes of mania significantly correlated with poor performance on measures of attention, executive function, and verbal memory of bipolar subjects of alcohol dependent.

Conclusion: The lifetime duration of bipolar illness adversely affects neurocognition. This relationship between this impairment and to lifetime duration of illness raises the possibility that early diagnosis and treatment could reduce the degree of neurocognitive impairment.

Key words: Alcohol, Bipolar, Memory, Neurocognitive, Psychiatric disorders

INTRODUCTION

Bipolar disorders are a large group of psychiatric disorders with signs and symptoms of pathological emotional disturbances, present over weeks to months, that represent a marked decline in a person's activities of daily living and tend to recur, often periodically or cyclically.[1] The prevalence of bipolar disorder is approximately 1% in the general population and studies have shown that the lifetime prevalence of bipolar disorders may be around 5%. In Bipolar disorders, a patient is said to be euthymic when the Hamilton Depression Scale score is below 7 and the Young Mania Rating Scale score is below 6 for 3 consecutive monthly assessments just before neuropsychological testing.[2]

Bipolar disorders are often associated with other comorbid disorders. Lifetime psychiatric comorbidity in bipolar disorders is 50–70%. The comorbidities associated with bipolar disorders are substance use disorders, anxiety disorders, personality disorders, and attention-deficit hyperactivity disorder. These comorbidities affect the course, severity, treatment response, and disease outcome.

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In addition, there is a strong association between bipolar disorders and alcohol dependence. Hence, there is a high prevalence of alcohol dependence in bipolar disorders, which might be due to the emotional instability leading to increased consumption of alcohol.[3] The severity of alcohol use-related disorders in bipolar patients is more disabling and has a damaging effect on the course of bipolar disorders. Therefore, the course of illness in patients with bipolar disorders and comorbid alcohol dependence may be very severe, and their long-term recovery is also poor.

Cognition includes attention, memory, language, orientation, praxis, executive function, judgment, and problem-solving. Hence, cognition disorders can affect personal, occupational, and social functioning.[1] In bipolar disorders, cognitive impairments in several domains are present not only during acute mood episodes such as manic, hypomanic, and depressive episodes but also during euthymic periods.[4] Neuropsychology research shows that significant cognitive impairment persists into euthymic periods, especially in patients with multiple episodes.[3] Some studies show that there is a significant cognitive impairment in domains such as attention, executive function, immediate memory, and verbal and visuospatial declarative memory in euthymic bipolar patients.[5]

In alcohol-related disorders, cognitive deficits in abstract reasoning, non-verbal learning, and perceptual-motor abilities may occur and slow to resolve the deficits in skills involving processing memory, problem-solving, and new learning ability. In bipolar disorder patients with comorbid alcohol dependence, cognitive deficits occur in executive functions and verbal memory. This deficit is more severe in patients with bipolar disorders and comorbid alcohol dependence.[6] Neuropsychological deficits associated with both bipolar disorders and alcohol dependence contribute to impairment of greater severity in patients who have bipolar disorder with comorbid alcohol dependence. The cumulative cognitive deficits contributed by bipolar disorder and alcohol dependence may lead to a severe cognitive impairment that interferes with the patient's recovery and overall functional ability.[4]

Many studies have demonstrated cognitive impairment in depressive, manic, or hypomanic episodes.[7] Studies about cognitive impairment in bipolar patients in the euthymic state with alcohol dependence are limited. Therefore, the purpose of this study is to evaluate cognitive functioning in euthymic bipolar individuals with and without alcohol dependence.

Aim

The aim of the study was to assess neurocognitive functioning in remitted bipolar individuals with and without a history of alcohol dependence and normal population.

MATERIALS AND METHODS

A comparative study was conducted at the Institute of Mental Health Hospital Chennai.

Study Period

Informed consent was obtained from 99 patients after a proper explanation of the purpose and procedure of the study.

Inclusion Criteria

The following criteria were included in the study:

Group 1: Subjects between the ages 20 and 55 years who are diagnosed to have Bipolar affective disorder and alcohol dependence as per ICD 10, who have been euthymic for at least 3 consecutive months, and who have been identified as alcohol dependent should be abstinent for 3 consecutive months at the time of interview. Group 2: Subjects between the ages 20 and 55 years, diagnosed with the bipolar affective disorder as per ICD-10 and without prior history of alcohol abuse or dependence, and who have been euthymic for at least 3 consecutive months. Group 3: Subjects aged 20–55 years and normal population.

Exclusion Criteria

The following criteria were excluded from the study:

All groups with a history of head injury and loss of consciousness for more than 1 h, H/o seizure disorder, H/o other psychiatric disorder, and H/o comorbid physical conditions.

To collect data regarding their characteristics such as name, age, sex, marital status, and education, using a patient questionnaire. Furthermore, collect disease-related information-duration of illness, number of episodes, duration of treatment etc. collected from the patients. YMRS and HAMD are to be administered to confirm euthymia in both groups.

Administration of neuropsychological tests in both groups to assess three domains of neurocognition, that is, Wisconsin card sorting test for executive functions; Digit Span Backwards and Digit Span Forwards for Attention, N back test for verbal memory.

The Independent *t*-test and Mann–Whitney U test, and Fisher's test were used to analyze sociodemographic data. In addition, Spearman's correlation coefficient is used to compare the course of illness and cognitive function.

RESULTS

The mean age of subjects in the cases Group A is 32.2 years. The mean age of subjects in cases Group B s 33.5 years. The mean age of subjects in control is 33.8 years.

In education, three groups have predominantly completed higher secondary education. In comparing occupation between groups, there is no statistical significance between Groups A and B ($P = 0.44$). However, there is significance in comparing Group A and the controls ($P = 0.01$) and between Group B and the controls ($P = 0.01$). In comparing married status between groups, there is no statistical significance between Groups A and B ($P = 0.67$) and B and C ($P = 0.15$). However, there is significance in comparing Group B and the controls ($P = 0.05$) [Table 1].

In Group A, the mean age of onset of alcohol use is 17.1 years and the mean duration of alcohol use is 12.6. There is no significant difference in the onset and duration of illness and depressive episodes between groups, but significance in manic episodes. On comparison of all parameters between bipolar alcohol-dependent (Group A) and bipolar alcohol-non-dependent (Group B) was not statistically significant. Still, when both groups were compared with the control group, they were statistically significant [Table 2].

The age of onset of bipolar illness is not significantly correlated with performance on measures of attention, executive function, and verbal memory of bipolar alcohol-dependent subjects.

Table 1: Distribution of patients characteristics in the study

Parameters	Groups		
	Alcohol dependent (%)	Alcohol non-dependent (%)	Control (%)
Education			
Illiterate	4 (10.3)	0	0
Primary	5 (12.8)	6 (15)	0
Secondary	7 (17.9)	5 (12.5)	4 (20)
Higher sec	15 (38.5)	14 (35)	10 (50)
Diploma/IT	5 (12.8)	3 (7.5)	1 (5)
Graduate	3 (7.7)	12 (30)	5 (25)
Occupation			
Unemployed	13 (33.3)	11 (27.5)	1 (5)
Unskilled	6 (15.4)	9 (22.5)	11 (55)
Semi-skilled	4 (10.3)	1 (2.5)	0
Skilled/Farmer	11 (55)	12 (30)	3 (15)
Clerical/shop owner	3 (7.7)	2 (5)	0
Semi-profession	0	1 (2.5)	4 (20)
Professional	2 (5.1)	4 (10)	1 (5)
Married status			
Married	14 (35.9)	18 (45)	13 (65)
Unmarried	22 (56.4)	20 (50)	5 (25)
Separated	3 (7.7)	2 (5)	2 (10)

The duration of illness of bipolar disorder significantly negatively correlated with performance on measures of attention, perseverative error, conceptual response, and total error of executive function and Hits 1 and 2 of N Back test of bipolar subjects with alcohol-dependent. In addition, the duration of illness of bipolar disorder significantly negatively correlated with performance on measures of perseverative error and total error of executive function and Hits 1 and 2 of N Back test of bipolar subjects with alcohol non-dependent [Table 3].

In alcohol dependent group, the number of episodes of mania significantly correlated with poor performance on measures of attention, executive function, and verbal memory of bipolar subjects of alcohol dependent.

In the alcohol-non-dependent group, the number of episodes of mania significantly correlated with poor performance on measures of attention, executive function, and verbal memory of bipolar subjects with alcohol-non-dependent [Table 4].

Table 2: Mean parameters of the study

Parameters	Group A	Group B	*P*-value
Onset of illness	24.8±3.8	25.5±4.3	0.44
Duration of illness	7.3±2.7	7.9±4.0	0.43
Manic episodes	5.8±3.9	3.3±2.1	0.001
Depressive episodes	0.4±1.0	0.3±0.8	0.59

Parameters	Group A	Group B	Control	*P*-value
Digit span forwards	5.5±0.9	5.3±1.1	6.9±0.7	0.48
Digit span backwards	3.3±0.7	3.3±0.8	4.5±0.5	0.96
Digit span test total standard score	91.7±8.1	89±8.8	102.1±3.0	0.15
WCST total error	88.6±8.0	89.2±10.4	106.1±6.4	0.76
WCST perseverative error	86.4±8.4	86.5±11.6	116.5±16.8	0.97
Non-perseverative error	97.1±5.8	96.9±7.4	93.3±3.5	0.91
WCST conceptual response	84.8±13.0	87.8±8.2	100.3±3.9	0.23
N back 1 hits	5.8±1.6	5.1±1.9	8±0.7	0.08
N back 2 hits	3.7±1.7	3.2±2.1	6.9±0.9	0.31
N back 1 error	3.8±1.9	3.2±1.6	1.1±0.8	0.36
N back 2 error	5.8±2.1	5.4±1.7	2.2±0.9	0.11

Table 3: Correlation of duration of illness for Group A and B

Parameters	Group A	P-value	Group B	*P*-value
Digit forwards	−0.605	<0.001	−0.173	0.29
Standard score	−0.469	0.002	−0.013	0.93
Total error	−0.690	<0.001	−0.377	0.01
Perseverative error	−0.503	0.001	−0.317	0.04
Non-perseverative error	−0.015	0.92	−0.198	0.22
Conceptual response	−0.690	<0.001	−0.173	0.29
N back 1 hits	−0.555	<0.001	−0.398	0.01
N back 2 hits	−0.633	<0.001	−0.367	0.02
N back 1 error	−0.015	0.92	0.130	0.42
N back 2 error	0.092	0.57	0.119	0.47

Table 4: Correlation of manic episodes for Group A and B

Parameters	Group A	*P*-value	Group B	*P*-value
Digit forwards	−0.553	<0.001	−0.475	0.002
Standard score	−0.452	0.005	−0.497	0.001
Total error	−0.629	<0.001	−0.564	<0.001
Perseverative error	−0.537	<0.001	−0.529	<0.001
Non-perseverative error	0.078	0.63	−0.063	0.70
Conceptual response	−0.618	<0.001	−0.570	<0.001
N back 1 hits	−0.611	<0.001	−0.566	<0.001
N back 2 hits	−0.482	0.002	−0.644	<0.001
N back 1 error	0.393	0.013	0.14	0.38
N back 2 error	0.305	0.05	0.11	0.50

DISCUSSION

In our study, the mean age of subjects among the three groups was 32–33 years, and there were no significant differences between the two groups in educational status. On comparing the occupational status of alcohol-dependent and non-dependent bipolar subjects, predominantly alcohol-dependent bipolar subjects were unemployed, whereas the alcohol-non-dependent bipolar subjects were mostly employed. Kumar *et al.*[8] study show that bipolar patients with substance use were predominantly unemployed.

In our study, bipolar patients with alcohol dependence were predominantly unmarried, consistent with Kumar *et al.*[8] study. However, Chaudhury *et al.*[9] demonstrated that bipolar patients with alcohol dependence are predominantly married. This study revealed that attention, executive functions, and verbal memory are impaired in both alcohol-dependent and non-dependent bipolar groups when compared to controls ($P < 0.001$). There is no significant difference between the two groups of bipolar subjects.

Von Gorp *et al.*[3] study reveals that only the bipolar group with alcohol dependence shows significantly worse performance than alcohol non-dependent and controls on measuring frontal lobe functioning. The author explains that it might be caused by the direct effects of alcohol on bipolar subjects who are alcohol dependent and due to which they have a more malignant form of bipolar disorder. Sanchez-Moreno *et al.*[10] studies of comparison between the neurocognitive functioning of bipolar patients with a history of alcohol abuse or dependence and without such history showed that cognitive dysfunction is more strongly associated with bipolar disorder than with a history of alcohol dependence or abuse. Bipolar patients with a history of alcohol abuse or dependence have greater difficulty in inhibitory control due to higher impulsivity.

Robinson and Ferrier[11] also demonstrated poor performance in executive functions, particularly interference. Levy *et al.*[12] also showed severe impairment in executive functions in bipolar disorder with alcohol dependence regardless of the euthymic state. Similar findings were demonstrated by Marshall *et al.*,[13] who showed poorer performance of conceptualization in bipolar disorder with alcohol use. In our study, the subjects in the bipolar disorder group with alcohol dependence had young onset of alcohol use (17.1 years), and the mean duration of alcohol use was 12.6 years. Strakowski *et al.*[14] suggested that bipolar subjects with a young onset of alcohol use would present more frequent episodes and a worse course of bipolar disorder.

In our study, there were no significant differences while comparing the age of onset of illness between alcohol-independent bipolar subjects and alcohol-dependent bipolar subjects. Furthermore, there was a significant negative correlation while comparing the duration of illness and the number of episodes of bipolar disorder with bipolar subjects with and without alcohol dependence. This explains that when the duration of illness of bipolar disorder increases, performance in cognitive domains decreases. Alcohol-dependent bipolar subjects have more cognitive impairment (Attention, total error, preservative error, conceptual response of executive function, and Hits 1 and 2 of N Back Test) than non-alcohol-dependent bipolar subjects (total error, preservative error of executive function, and Hits 1 and 2 of N Back Test) on correlating with a duration of illness.

Our results explained that several manic episodes negatively correlated with cognitive performances in alcohol-dependent and non-dependent bipolar groups. This finding suggests that the aggregate duration of illness/episodes has more effect on cognitive function. In addition, Von Gorp *et al.*[3] demonstrated that longer duration of illness and number of episodes of mania significantly correlated with poorer performance on measures of executive function. However, no significant differences were seen in depressive episodes between these two groups.

Karry *et al.*[15] demonstrated that there were no differences in cognitive functions between bipolar patients with >10 years of duration of illness compared to those with <10 years of illness. Denicoff *et al.*[6] suggest a relationship between a greater number of episodes, a longer duration of illness, and poorer neurocognitive functioning in subjects with bipolar disorder. Zubieta *et al.*[16] and Winokur *et al.*[17] suggest that neurocognitive impairment in dually diagnosed subjects may be associated with the severity of the bipolar disorder. In addition, mood episodes of greater severity and duration have been independently associated with poor neurocognitive functioning and cooccurring substance use disorder.

CONCLUSION

There is an increased number of manic episodes in alcohol-dependent bipolar patients. Euthymic bipolar subjects have impaired function on attention, executive function, and verbal memory. However, there is no statistically significant impairment of cognitive function in euthymic bipolar subjects with alcohol dependence. The lifetime duration of bipolar illness adversely affects neurocognition. This relationship between this impairment and to lifetime duration of illness raises the possibility that early diagnosis and treatment could reduce the degree of neurocognitive impairment.

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Original Article

Clinicopathological Profile of Carcinoma Cervix and Their Impact on Survival of Patients

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Abstract

Introduction: Cervical carcinoma is one of the leading causes of death in female patients. In India, cervical cancer accounted for 9.4% of all cancers and 18.3% (123,907) of new cases in 2020. It still is among the most common cancers in India and a leading cause of cancer-related deaths in women in lower- and middle-income countries. FIGO stage, histological types, depth of stromal invasion, lymph vascular space invasion, and lymph nodes metastasis are aggressive characteristics of cervical cancer, which are regarded as significant factors for treatment, prognosis, and recurrence and have a great impact on survival.

Objectives: This study aimed to analyze the clinicopathological characteristics of women with cervical cancers in Kashmir and their impact on survival.

Materials and Methods: It was a retroprospective study which was conducted in tertiary care hospital from year January 2017 to December 2021. A total of 31 patients histologically confirmed were taken for this study. The data were subdivided into two groups with histology adenocarcinoma and squamous cell carcinoma, respectively. Patients' characteristics were analyzed under the following parameters age, FIGO stage (I, II, III, and IV), grade (well-differentiated, moderately differentiated, poorly differentiated, tumor histology (squamous, and adenocarcinomas), nodal status (node-positive, node-negative), lymphovascular invasion, and correlated with and their impact on survival of patients.

Results: A total of 31 patients with cervical cancer were analyzed in the data. The majority of patients in the squamous cell carcinoma (group) were in the age group of 60 (35.29%) and 40–49 (35.29%) and while, in the adenocarcinoma group (Group B), the majority of patients were in the age group of 60 (35.71%), followed by 40–49 (28.57%). In Group A, majority of patients were having IIB stage 6 (35.29%) and in Group B, majority were having stage IIA 6 (42.85%). In Group A, 11 patients (64.70%) received concurrent chemoradiation and brachytherapy, while 3(17.64%) received adjuvant radiation and 3(17.64%) received chemotherapy. In Group B, two patients (14.28%) received adjuvant radiotherapy and 2 (14.28%) received chemotherapy and nine received concurrent chemoradiation followed by brachytherapy (64.28%), while 1(7.14%) received radiation followed by chemotherapy. At 1 year of follow-up 14 (82.35 %), patients were diseases free and 3(17.64%) had metastasis, 1 (5.88%) had died in Group A, while in Group B, two patients (14.28%) died, six patients (42.85%) were disease free, and one patient (7.14%) had local recurrence and five patient (35.17%) had metastasis. The disease-free survival was 33 months for Group A and 24 months for Group B. Overall survival percentage was more in Group A which is 59 months and 21 months for Group B.

Conclusion: Our results suggest that histology, lymphovascular invasion, parametrial involvement, and nodal involvement are independent predictors of shorter survival in patients with cervical adenocarcinoma. Adenocarcinoma was associated with a worse prognosis compared to squamous, particularly for patients who require post-operative treatment; such patients may benefit from individualized post-operative treatments that differ from those applied for squamous.

Key words: Carcinoma, Lymphovascular invasion, Survival

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INTRODUCTION

Cervical carcinoma is one of the leading causes of death in female patients. As per Globocan 2020, 604,100 new cases of cervical cancer were detected globally in 2020 and 341,831 deaths were attributed to this malignancy. In India, cervical cancer accounted for 9.4% of all cancers and

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18.3% (123,907) of new cases in 2020. It still is among the commoner cancers in India and a leading cause of cancer-related deaths in women in lower- and middle-income countries[1] Although the age-standardized incidence rate of cervical cancer decreased substantially by 39.7% (95% UI 265–57.3) from 1990 to 2016, it is the second leading cause of cancer deaths for females in 12 Indian states.[2] The peak age of incidence of cervical cancer is 55–59 years, and a considerable proportion of women report in the late stages of the disease.[3] The situation is more alarming in the rural areas, where the majority of women are illiterate and ignorant about the hazards of cervical cancer as well as health-care resources are scarce as reported.[4] The incidence of cervical carcinoma is low in Kashmir as per studies.[5]

In addition to HPV infection, early coitus, number of pregnancies, genital hygiene, use of oral contraceptives, nutritional status, smoking, etc., are associated with the development of cervical cancer. Various methods of treatment are used for cervical carcinoma depending on the stage. The previous studies have revealed that age, FIGO stage, histologic types, depth of stromal invasion, lymph vascular space invasion, and lymph nodes metastasis are aggressive characteristics of cervical cancer, which are regarded as significant factors for treatment, prognosis, and recurrence.[6,7] Consequently, this study aimed to analyze the clinical pathological characteristics of women with cervical cancers in Kashmir and their impact on survival.

PATIENTS AND METHODS

This study was performed in the Department of radiation oncology, Government medical college Srinagar, Kashmir India. It was a retrospective analysis of patients with cervical carcinoma. A total of 50 patients were registered at our hospital out of which 31 patients were taken for the study and the remaining patients were excluded due to a lack of follow-up. The study population included all the histopathologically confirmed 31 cases of cervical cancer between January 2017 and December 2021. The study group was divided into two groups; Group A included 17 patients with squamous cell carcinoma histology and Group B included 14 patients with adenocarcinoma histology. The sociodemographic, clinical, radiological, and histopathological findings were retrieved into a structured pro forma. The other details included the type of treatment provided and post-treatment assessment, patients, and characteristics were analyzed under the following parameters age, FIGO stages grade (well-differentiated, moderately differentiated, and poorly differentiated), tumor histology, nodal status, lymphovascular invasion, and survival. In addition, treatment modalities such as surgery, radiotherapy, and chemotherapy were also included in the study.

The follow-up was done at 3 monthly for 1 year and then 6 monthly for another 2 years and then annually, by interval history, gynecological examination, and by radiologically. Adjuvant radiotherapy or concurrent chemotherapy was given in patients with high post-operative risk factors.

Results: total of 31 patients with cervical cancer were analyzed in the data. Table 1 summarizes the demographic and clinicopathological characteristics of the study. The majority of patients in Group A were in the age group of 60 (35.29%) and 40–49 (35.29%), while, in Group B, majority of patients were also in the age group of 60 (35.71%) and 40–49 (28.57%), respectively.

The majority of patients in Group A were having stage IIB 6 (35. 29%), while 3 (17.64%) were having stage IIA, 4 (23.52 %) were having stage III, 2 (11.57%) were having Ib2, and one patient had stage IVA (5.88%) and 1(5.88%) had IVB. However, in Group B, majority of patients 6 (42.85%) were having II A, followed by 4 patients(28.57%) who had stage II B and 1 patient had stage III (7.14%), and 1 had stage IVB (7.14%) and 2 (14.28%) had stage Ib2.

The majority of patients in Group A were having well-differentiated histology 7 (41.17%), while, in Group B, majority were moderately differentiated 8 (57.14.0%), as shown in Table 1.

Out of 17 patients in Group A, 11 patients (64.70%) received concurrent chemoradiation followed by brachytherapy,

Table 1: Demographic and clinicopathological characteristics

Demographic profile					
Variables	**Category**	**Histology**			
		GROUP A (Squamous cell carcinoma)		**GROUP B (Adenocarcinoma)**	
		***n* (17)**	**%**	***n* (14)**	**%**
Age	<39	1	5.88	4	28.57
	40–49	6	35.29	4	28.57
	50–59	4	23.52	1	7.14
	60+	6	35.29	5	35.71
Mean±SD		53±11.85		47±12.80	
FIGO	1b2	2	11.57	2	14.28
	IIA	3	17.64	6	42.85
	IIB	6	35.29	4	28.57
	III	4	23.52	1	7.14
	IVA	1	5.88	0	0.00
	IVB	1	5.88	1	7.14
Grade	Moderately differentiated.	6	35.29	8	57.14
	Poorly differentiated	4	23.52	2	14.28
	Well-differentiated	7	41.17	4	28.57
Total		17		14	

while three patients (17.64 %) received adjuvant radiation and three patients (17.64%) received chemotherapy, while as in Group B, two patients (14.28%) received adjuvant radiotherapy and two patients (14.28%) received chemotherapy, nine patients (64.28%) received concurrent chemoradiation and brachytherapy, and 1 (7.14%) received chemotherapy after radiation, as shown in Table 2.

In Group A, seven patients (41.17%) had undergone surgery, four patients (23.52%) out of seven had lymphovascular invasion, and four patients (23.52%), out of seven were lymph node-positive; however, in Group B, eight patients (57.14%) had undergone surgery, five patients (35.71%), out of eight had lymphovascular invasion and all 8 (57.14%) patients had lymph node-positive.

Follow-up at 3 months, 15 patients (88.23%) had no evidence of diseases and two patients (11.76%) had residual diseases in Group A, while, in Group B, nine patients (64.28%) had no residual diseases; however, five patients (35.71%) had residual diseases. After a follow-up at 6 months, 14 patients (82.35%) had no evidence of diseases and 3 (17.64%) were metastatic in Group A, while, in Group B, 11 patients (78.57%) had no evidence of diseases, while three patients (21.42%) had metastasis.

At 1 year of follow-up, in Group A, 14 (82.35%) patients were diseases free and two patients (11.76%) had metastasis, and 1 (5.88%) had died, while, as in Group B, two patients (14.28%) died, six patients (42.85%) were disease free, and one patient (7.14%) had local recurrence; however, five patients (35.17%) had metastasis.

Statistic

Survival analysis was done using SPSS 26, overall survival Kaplan–Meyer survival analysis, log-rank (Mantel-Cox) test of equality for survival distribution was used to explore P value <0.05, was considered statistically significant. Overall survival percentage was more in Group A which is 59 months and 21 months for Group B. Mean survival time was 29.3 months for Group A and 22.2 months for Group B and that was a significant difference between the survival of the two groups (P = 0.018). The disease-free survival was 33 months for Group A and 24 months for Group B. There was a statistically significant difference between the two histological types in terms of DFS (P = 0.012).

TABLE 2: TREATMENT, RISK FACTORS AND OVERALL SURVIVAL

	GROUP A (Squamous cell carcinoma. N=17)		GROUP B (Adenocarcinoma N=14)	
Surgery				
No	10	58.82%	6	42.85%
Yes	7	41.17%	8	57.14%
Lymph Node				
Yes	4	23.52%	8	57.14%
No	13	76.47%	6	38.46%
Lymphovascular Invasion				
Yes	4	23.52%	5	35.71%
No	13	76.47%	9	64.28%
Treatment				
Chemotherapy	3	17.64%	2	14.28%
Concurrent chemoradiation+Brachytherapy	11	64.70%	9	64.28%
Adjuvant Radiation+Brachytherapy	3	17.64%	2	14.28%
Radiation+Chemotherapy+Brachytherapy	0	0.00%	1	7.14%
Follow-up at 3months				
No evidence of residual disease	15	88.23%	9	64.28%
Residual disease	2	11.76%	5	35.71%
Follow-up at 6 month				
Metastatic	3	17.64%	3	21.42%
No evidence of disease	14	82.35%	11	78.57%
Follow-up at 12months				
Death	1	5.88%	2	14.28%
Disease free	14	82.35%	6	42.85%
Local recurrence	0	0.00%	1	7.14%
Metastasis	2	11.76%	5	35.17%
Survivalat2 years				
Alive	11	64.70%	7	50.00%
Died	4	23.52%	4	28.57%
Metastasis	1	5.88%	1	7.14%
Survival at 3 years				
Alive	10	58.82%	2	14.28%
Disease free	1	5.88%	3	21.42%
Died	1	5.88%	3	21.42%

In this study, we found that advanced clinical stage, vascular invasion, parametrial invasion, and lymph node metastasis were high-risk factors influencing the prognosis of cervical cancer. However, prognosis had no significant correlation with age and histological grade. Although treatment for adenocarcinoma and squamous carcinoma was the same, they seemed to respond differently to treatment, high nodal positivity and lymphovascular invasion seemed to affect survival more.

DISCUSSION

Cervical cancer is the most common malignancy in developing nations after breast cancer among malignant tumors in women. There are still unresolved controversies in domestic and foreign studies on the prognostic factors of cervical cancer, especially in terms of pathological factors which are consistent with findings by Lapresa *et al*.[8] Therefore, exploring the prognostic factors of cervical cancer, improving early detection rate, and developing effective treatment measures to improve survival rate are of utmost importance.

In our study, 31 patients were taken in the final analysis, out of which 17 patients (54.83%) were having (Group A) squamous cell carcinoma histology and 14 patients (45.16%) were having (Group B) adenocarcinoma histology which is similar to the study conducted by Vinh-Hung *et al*.[9] The mean age in squamous cell carcinoma group was 53 ± 11.85 belonging to the range of <39–60+ and the mean age in adenocarcinoma group was 47 ± 12.80 ranging from <39 to 60+ which is similar to study conducted by Sreedevi *et al*.[3]

In our study, most of the patients in Group A had stage IIB 6 (35.29 %) and in Group B stage IIA (42.85%) at presentation, which is similar to a study conducted by Mohumud *et al*.[10] that staging has a prognostic value. The proportion of patients in Group A who underwent surgery was 41.17% and post-operative lymphovascular invasion was found in 23.52% and node positivity was seen in 23.52%. However, in Group B, 57.14% of patients who underwent surgery, 35.71% patients had lymphovascular invasion and 57.14% patients had lymph node positivity which is similar to a study conducted by Wang *et al*.[11]

At follow-up of 3 months in Group A, 88.23% were disease free and 11.76% were having residual disease, while in Group B, 64.28% were disease free and 35.71% were having a residual disease. Patients in both groups having residual were subjected to chemotherapy and again followed at 6 months, it was found that in Group A, 82.35% were disease free and 17.64% had developed metastasis, while, in Group B, 78.57% were disease free and 21.42% had metastasis.

At follow of 1 year, 82.35% were disease free, 11.76% of patients had metastasis, and 5.88% of patients had died in Group A, while, in the adenocarcinoma group, 42.85% of patients were disease free, 14.28% of patients had died, 7.14% patients had local recurrence, and 35.17% had metastasis, which are similar to studies conducted by Hu *et al*.[12]

Overall survival for Group A was 51%, while, in Group B, it was 21%. Disease-free survival for Group A was 33 months and 24 months for Group B, these findings are consistent with studies done by Yamauchi *et al*.[13] who found that despite giving the same treatment adenocarcinoma tends to behave differently.

Investigations comparing the prognosis of cervical adenocarcinoma with squamous cell carcinoma came up with varying results, with certain studies reporting adenocarcinoma tends to have a poorer prognosis compared to squamous cell carcinoma as reported by Nakanishi *et al*.[14-18] and while a study done by Park *et al*.[14-18] reported no statistically significant differences between the two groups.

Lymph node metastasis is commonly more aggressive in adenocarcinoma compared to squamous cell carcinoma and some studies reported a higher incidence of lymph node metastasis and poorer prognosis in adenocarcinoma compared to squamous after controlling for stage and tumor size. Therefore, a shorter progression-free survival was found in patients with adenocarcinoma, especially those in the early FIGO stage. The study by Zheng *et al*.[19] found that 91% of the literature considered lymph node metastasis as an independent risk factor for poor prognosis. In addition, we also demonstrated that positive post-operative pathological factors, such as lymphovascular invasion, lymph node metastases, and parametrial involvement, could worsen the prognosis of adenocarcinoma patients more as compared with squamous. A study conducted by Zheng *et al*.,[19] found that vascular invasion is also an important factor associated with prognosis, our study also reveals similar results.

Among patients who received postoperative irradiation alone, the adenocarcinoma Group B exhibited a significantly poorer prognosis compared to the squamous cell Group A; there was no significant difference between the two groups among patients who received postoperative chemotherapy or concurrent chemoradiation. Similarly, patients with adenocarcinoma experienced more local failure in our study. We found that patients with Group B were more

likely to have distant failure. Cervical adenocarcinoma is more radio resistant compared to squamous suggesting that post-operative irradiation alone does not improve overall survival in patients with cervical adenocarcinoma which is also similar to a study done by Margolis *et al*.[19,20]

The limitations of this study are that it was a retrospective and single-center study and, therefore, had a lower level of evidence. In addition, the sample size was small.

CONCLUSION

Our results suggest that lymphovascular invasion, parametrial involvement, and nodal involvement as independent predictors of shorter survival in patients with cervical adenocarcinoma. Adenocarcinoma was associated with a worse prognosis compared to squamous, particularly for patients who require post-operative treatment; such patients may benefit from individualized postoperative treatments that differ from those applied for squamous.

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Original Article

Prevalence and Risk Factors of Dry Eye Disease: Ocular Surface Disease Index and Tear Film Break up Time Based Study

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Abstract

Introduction: Dry eye disease (DED) is one of the common ophthalmological conditions and is a growing public health problem.

Aims: The aims of this study are to assess the prevalence of DED and its associated risk factors.

Materials and Methods: A total of 600 patients with age more than 20 years who visited the ophthalmology outpatient department of a tertiary care center were selected randomly. The study design was a prospective, cross-sectional, and observational study. An ocular surface disease index (OSDI) questionnaire was administered to all participants and individuals with OSDI score >13 was further evaluated with tear break-up time (TBUT). Diagnosis of DED was made on the bases of OSDI score more than 13 and TBUT <10 s. The data were compiled and subjected to statistical analysis.

Results: Prevalence of dry eye in our study was 33.66%. Use of Visual display terminal, outdoor occupation, refractive surgery, use of topical anti-glaucoma drugs, use of contact lens, smoking, connective tissue disorder, and diabetes mellitus were identified as significant risk factors associated with DED.

Conclusions: DED is a common condition. We recommend the screening of all out-patients by TBUT, which is a simple and reliable test. Patients should be educated regarding the various risk factors associated with DED and about lifestyle modifications.

Key words: Dry eye disease, Ocular surface disease index, Tear break-up time

INTRODUCTION

Dry eye disease (DED) is a disease of the ocular surface commonly presented in clinical practice. Tear Film and Ocular Surface Society Dry Eye Workshop II report published in July 2017 defined DED as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms in which tear film instability, hyperosmolarity, ocular surface inflammation, and neurosensory abnormalities play etiological roles.[1]

The core pathophysiological process of dry eye is contributed by reduced aqueous tear flow and increased evaporation leading to hyperosmolarity. Hyperosmolarity further damages the epithelium of ocular surface and sets off a cascade of inflammatory pathways within surface epithelial cells. After inflammatory pathways sets off the mediators, there occurs loss of goblet cells and epithelial cells, epithelial glycocalyx damage, apoptotic cell death, mucus production deficiency leading to punctate epitheliopathy of dry eye, and tear film instability. All these factors ultimately lead to early break up of tear film.

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Vicious cycle events are completed in this way by tear film break up which amplifies hyperosmolarity and ocular surface damage.[2]

In a study conducted in India in 2010, the prevalence of dry eye based on ocular surface disease index (OSDI) was found to be 29.25%.[3] A survey conducted by an American academy of ophthalmology in 2014 reported that around 30% of patients seeking treatment from an ophthalmologist have symptoms consistent with DED.[4]

Dry eye causes a significant discomfort on the everyday life, which indirectly influence overall economy of a nation. To the best of our knowledge, no study has been conducted to describe the prevalence of DED in this border area of India, this study was conducted to assess the prevalence of DED and to identify the associated risk factors.

MATERIALS AND METHODS

We conducted a prospective, cross-sectional, hospital-based, and observational study involving 600 patients who visited ophthalmology outpatient department at a tertiary care center. Patients of more than 20 years of age with various complaints may or may not related to dry eye were randomly selected from the outpatient department. Our study sample includes mixed population of both rural and urban areas The study was approved by the Institution Ethical Committee. Written informed consent from all the patients enrolled in the study was obtained in their vernacular language, in accordance with the Declaration of Helsinki.

Patients <20 years of age, patients with history of acute ocular infection; inflammation or allergic conjunctivitis, patients with gross lid abnormalities, and patients with history of extra or intraocular surgery within past 6 months were excluded from the study.

Comprehensive history pertaining to dry eye and history of visual display terminal (VDT) usage including television, smartphones, tablets, and laptops was obtained from all the patients.

Data regarding the systemic and ocular risk factors causing or triggering DED such as diabetes, thyroid disorder, connective tissue disease, use of topical anti-glaucoma drugs, refractive surgery, ocular trauma, contact lens use, and smoking were recorded.

A scientifically validated OSDI questionnaire was administered to all participants to assess the symptoms of dry eye. The questions were explained to the patients in their vernacular language by a single trained ophthalmology resident. The OSDI questionnaire is a subjective symptom questionnaire that includes 12 items, with each question given a score ranging from 0 (none of the time) to 4 (all of the time). The patients had to assign a score based on duration of symptoms experienced over the preceding week. The final score was calculated by multiplying the sum of all the scores with 25 and then dividing the total by number of questions answered.[5]

Patients with OSDI score >13 further underwent a general ophthalmic assessment along with slit lamp examination and tear break-up time (TBUT). TBUT was performed in all participants by a single observer.

Tear film break up time: It was used to assess the stability of precorneal tear film. It is considered to be a reliable and repeatable test for dry eye and is minimally invasive.[6] TBUT has been reported to be low in different types of dry eye including keratoconjunctivitis sicca, mucin deficiency, and meibomian gland disease.[7] It was performed by moistening a 2% fluorescein strip with normal saline and placing it in the inferior fornix in non-anesthetized eye. The patient was asked to blink eyes once or twice. The tear film was evaluated using broad beam of slit lamp with a cobalt blue filter. The time interval from the last blink to the appearance of the first randomly distributed dry spot on the cornea was noted. The test was repeated thrice and the mean value was calculated. Value of <10seconds was considered as indicative of tear film instability.

Diagnosis of DED was made on the bases of OSDI score >13 and TBUT <10 s.

Statistical Analysis

Average of results of OSDI and TBUT of both eyes was considered for analysis purpose. The descriptive statistics were used to express data on terms of percentage.

$$\text{Prevalence of dry eye} = \frac{\text{Number of patients diagnosed with dry eye}}{\text{Total number of patients included in the study}}$$

RESULTS

A total of 600 patients participated in the study. The prevalence of dry eye in our study was 33.66%. The prevalence of dry eye among female patients was 38.65% and among male patients was 27.73%. The prevalence of

dry eye among urban population was 41.06% and among rural patients was 17.20%. We assessed the prevalence of dry eye among various occupation groups and found maximum prevalence of dry eye among computer operators (68.18%), the prevalence of DED was higher in individuals using VDT for >6 h (63.9%) followed by 2–6 h (62.7%) and <2 h (43.1%) users, thus showing high association of VDT use with DED.

[Table 1] shows prevalence of dry eye according to age, sex, place of residence, and occupation.

Systemic risk factors associated with dry eye was connective tissue disease (75%), thyroid disorder (60.7%), and diabetes mellitus (42.1%). The prevalence of dry eye in patients with history of topical anti-glaucoma drugs was 80%, refractive surgery 78.1%, contact lens use 62.5%, and in smokers 57.89%.

[Table 2] shows prevalence of various risk factors associated with DED.

Table 1: Prevalence of dry eye according to age, sex, place of residence and occupation

Demographic characteristics	Number of patients *n*=600	Dry eye presents *n*=202	Prevalence Percentage
Age in years			
20–29	69	22	31.88
30–39	130	53	40.76
40–49	139	61	43.88
50–59	107	35	32.71
60–69	90	19	21.11
70–79	40	8	20.00
>80	25	4	30.76
Gender			
Male	274	76	27.73
Female	326	126	38.65
Rural	186	32	17.20
Urban	414	170	41.06
Occupation			
Computer operator	66	45	68.18
Housemakers	189	38	20.10
Students	24	13	54.16
Office employees	96	44	45.83
Drivers	13	5	38.46
Farmers	126	42	33.33
Laborer/Factory worker	28	10	35.71
Others*	58	6	10.34

*Tailors, jobless, carpenter, electricians

Table 2: Prevalence of various risk factors in dry eye disease

Study factors	Number of patients	Dry eye patients	Prevalence percentage of dry eye
History of diabetes	76	32	42.1%
History of thyroid disorder	28	17	60.7%
History of connective tissue disease	8	6	75%
Use of topical anti-glaucoma drugs	35	28	80%
History of refractive surgery	32	25	78.1%
History of Contact lens use	8	5	62.5%
History of Smoking	19	11	57.89%

DISCUSSION

The prevalence of DED in various population and hospital-based studies varies between 7.7% to as high as 73.5%.[8,9] In our study, the overall prevalence of dry eye among patients of age 20 years and above was found to be 33.66%. Similar to this, a study conducted in Korea reported a prevalence of 33.2%.[10] Whereas, study conducted by Shah and Jani. observed the prevalence of DED as 54.3%.[11]

Maximum prevalence (43.88%) of dry eye seen in this study was in the age group of 40–49 years followed by 40.76% in age group of 30–39 years. A cross-sectional study in Jordan found a high association of dry eye symptoms in subjects with age >45 years.[12] Whereas, another study done in the year 2005 observed significantly higher prevalence of dry eye (36%) in the older age groups (>70 years), as compared to all other age groups.[13]

In our study, the dry eye was more prevalent among female (38.65%) than among males (27.73%). Similarly, female preponderance has been reported in the study done by Sahai and Malik.[13] However, a study done by Titiyal *et al*. in North India and a study done by Tseng *et al*. reported higher prevalence of dry eye in males than females.[14,15]

About 69% of our study population was from urban area, prevalence of dry eye was found to be more in urban patients (41.06%) than patients from rural area (17.20%). Similarly, more preponderance of dry eye among urban subjects was seen in a population-based dry eye study done by Lee *et al*.[16]

We found the highest prevalence of dry eye among computer operators and students (68.18% and 54.16%, respectively). This may be due to exposure to computers/mobiles screens as well as air conditioners at the same time. We also observed that maximum prevalence of DED in subjects with VDT use for more than 6 h (63.9%), followed by 2–6 h (62.7%) and <2 h (43.1%). A study done in 2005 also found higher prevalence of dry eye in computer users.[13] Another study done in North India reported that 89.98% of patients with 4 h or more of VDT usage were associated with severe dry

eye.[14] Thus, use of television, mobile phones, computers, and laptops for hours was observed to have a significant correlation with DED. This emphasizes the need for creating awareness among the students and computer users to adopt preventive measures.

About 31% of our study population consists of drives, farmers, and laborers, the prevalence of dry eye among them was 38.46%, 33.33%, and 35.71%, respectively. Khurana *et al*. too reported the prevalence of dry eye of 32% among farmers and 28% among laborers. This was probably due to their prolong exposure to excessive heat, sunlight, and dust.[17] In year 2015, a hospital-based study in South-east China also observed exposure to adverse environment as a risk factor for DED.[18] In contrast to our findings, a study conducted in 2010 reported that occupation had no effect on the risk of dry eye ($P = 0.952$).[3]

We found prevalence of dry eye of 75% among the patients of connective tissue disease. Among 28 patients who were having thyroid disorder, dry eye was found in 60.7%. Similarly, a study conducted by Shah and Jani and another study conducted by Galor *et al*. in United States observed higher risk of dry eye in patients of connective tissue disease and in patients of thyroid disorder in.[11,19] We found 42.1% prevalence of dry eye among the diabetic patients. This is consistent with a study conducted by Manaviat, who found the prevalence of 54.3% of dry eye among the patients of Type 2 diabetes.[20] In the present study, the prevalence of dry eye among patients on topical anti-glaucoma medication was eighty percent. This was consistent with the study conducted by Shah and Jani who also found the prevalence of dry eye of 72% among patients on topical anti-glaucoma medication.[11]

In the present study, the prevalence of dry eye among contact lens users was 62.5%. A study conducted in Japan in year 2011, Beaver Dam Offspring Study in 2014 and a study in Jordan 2016 also found contact lens use a risk factor for DED.[9,19,12] The prevalence of dry eye was 78.1% in patients with history of refractive surgery and 57.89% among the smokers in this study. A study conducted by Shah and Jani in Gujrat also found 60.4% prevalence of dry eye among patients with history of intraocular surgery and 60% prevalence of dry eye among smokers.[11]

Limitations

The main limitation of our study is that it is a hospital-based study which by itself increases the prevalence as compared to study done in a community. Further population-based studies need to be undertaken to assess the prevalence of DED more accurately and establish concrete etiological association with various risk factors.

CONCLUSIONS

High (33.66%) prevalence of DED in our study reflects it as a major burden among routine outpatients. Risk factors precipitating or worsening the DED include VDT use, contact lens use,outdoor occupations like farmers, laborer and drivers, connective tissue disease, thyroid disorder, diabetes mellitus, use of topical anti-glaucoma drugs, refractive surgery, and smoking. These contributing factors need to be emphasized for a more systematic targeted and effective approach toward DED. Identification of these factors not only would decrease ocular health burden but also minimize huge economic burden on the society.

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Original Article

Evaluation the Efficacy of 0.75% Ropivacaine with Dexamethasone Compared to 0.75% Ropivacaine with in Ultrasound Guided Ultrasound Guided Supraclavicular Brachial Plexus Block in Patients Undergoing Upper Limb Surgeries

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Abstract

Aim: The aim of the study was to evaluate the efficacy of 0.75% ropivacaine with dexamethasone compared to 0.75% ropivacaine in ultrasound guided supraclavicular brachial plexus block in patients undergoing upper limb surgeries.

Methods: A prospective, randomized, and controlled study is conducted in 60 ASA I and II patients undergoing upper limb surgeries under supraclavicular brachial plexus block were randomized in to two groups of 30 members each group, Group I – 0.75% ropivacaine (20 mL) plus 8 mg of dexamethasone. Group II – 0.75% ropivacaine (20 mL) plus 2 mL of normal saline.

Results: Onset of sensory block was assessed by pinprick method and motor blockade by modified bromage scale for every minute till complete blockade occurs. $P < 0.05$ was considered statistically significant. Results showed that demographic data are comparable between both groups. The study results showed that 0.75% ropivacaine with dexamethasone group had prolonged duration of sensory and motor blockade and longer duration for first rescue analgesia than 0.75% ropivacaine with normal saline group.

Conclusion: Group I (addition of dexamethasone group) prolong the motor block enhances the quality of block and duration of analgesia significantly when compared with control group (normal saline) in supraclavicular brachial plexus block.

Key words: 0.75% ropivacaine, Dexamethasone, Ultrasound-guided ultrasound guided supraclavicular brachial plexus block, Upper limb surgeries

INTRODUCTION

Brachial plexus block is a popular and widely employed regional nerve block of the upper extremity. Various approaches to brachial plexus block have been described such as interscalene, supraclavicular, infraclavicular, and axillary, but supraclavicular approach is the easiest and most consistent method for anesthesia and perioperative pain management in surgery below the shoulder joint. Supraclavicular brachial plexus block is an excellent technique in experienced hands. Pneumothorax, Hemothorax, Horner's syndrome, and phrenic nerve block are the potential complications. Dexamethasone has been studied as an adjuvant to local anesthetic in peripheral nerve block steroids have nerve block prolonging effects. They produce analgesia by blocking transmission of nociceptive myelinated c-fibers and suppressing ectopic neuronal discharge. They might bring about this effect by altering the function of potassium channels in the excitable cells. With ultrasound-guided technique vital structures in supraclavicular region can be easily identified in real time along with optimum local anesthetic spread even with low volume of local anesthetic drug.

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Aims and Objectives

The aim of the study was to evaluate the efficacy of 0.75% ropivacaine with dexamethasone compared to 0.75% ropivacaine in ultrasound-guided supraclavicular brachial plexus block in patients undergoing upper limb surgeries with respect to

1. Onset of sensory blockade and motor blockade
2. Duration of motor blockade
3. Duration of analgesia (time to first request for analgesic)
4. Quality of block
5. Complications/side effects if any

PATIENTS AND METHODS

After institutional approval, this randomized, controlled, clinical, control, and comparative study was conducted from April 2022 to December 2022 over a period of 999 months in the Department of Anesthesiology, Government General Hospital/Siddhartha Medical College, DR. YSR YSR YSR UHS, Vijayawada.

Inclusion Criteria

The following criteria were included in the study:

1. ASA Status I and II
2. Age between 18 and 65 years
3. Patients undergoing upper limb surgeries under supraclavicular brachial plexus block.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patient not willing to participate in the study
2. Patients with ASA grade >III
3. Patients with known hypersensitivity to local anesthetic drugs
4. Patients with coagulation abnormalities
5. Patients with pre-existing peripheral neuropathy
6. Infection at the site of injection.

Study Design

This prospective, randomized, and controlled study conducted on 60 ASA I and II patients undergoing upper limb surgeries under supraclavicular brachial plexus block who fulfilled inclusion criteria. The study was started after receiving institutional ethical committee approval and informed written consent from all the patients and they were randomly divided into two groups.

Two Groups

- Group I-20 mL of 0.75% ropivacaine plus 2 mL of dexamethasone (30 patients)
- Group II-20 mL of 0.75% ropivacaine plus 2 mL of normal saline (30 patients).

Procedure

The basal parameters pulse rate, respiratory rate, blood pressure, and spo2 were recorded before starting the case. Peripheral venous cannulation was done with 18G IV cannula in opposite arm and all the patients were preloaded with 10 mL/kg Ringer lactate solution. Each patient would be given 0.03mg/kg of midazolam intravenously (IV) as a premedication 15 min before beginning the block technique. Under strict aseptic precautions, all the patients received brachial plexus block through the ultrasound guided supraclavicular approach.

Time of injection was recorded as 0 h. In the two groups, the following parameters are noted.

1. Onset of sensory and motor blockade
2. Duration of motor blockade
3. Duration of post-operative analgesia (time to administration of rescue analgesic)
4. Quality of block
5. Side effects.

Continuously SpO_2 and pulse rate were monitored. Hemodynamic variables such hear rate, systolic and diastolic blood pressures, and mean arterial pressure were recorded every 15 min intraoperatively after block and every 1 h postoperatively for 6 h, and 2nd hourly for 12 h.

Sensory block was assessed by pinprick method. Assessment of sensory block was done at each minute after completion of drug injection in the dermatomal areas corresponding to median nerve, radial nerve, ulnar nerve, and musculocutaneous nerve till complete sensory nerve blockade.

Onset of sensory block

It was taken as the period from the time of injection of local anesthetic solution to the absence of pinprick sensation as experienced by the patient.

Sensory block was graded as:

- Grade 0: Sharp pin felt
- Grade 1: Analgesia, dull sensation felt (sensory onset)
- Grade 2: Anesthesia, no sensation felt (complete sensory block).

Duration of sensory block

It was taken as the period from the time of loss of pinprick sensation to the reappearance of pinprick sensation as revealed by the patient.

Duration of analgesia

It was taken as the time between the injection and the onset of pain and request for rescue analgesic. Rescue analgesia was given in form of inj. diclofenac sodium (1.5 mg/kg)

intramuscularly along with oral paracetamol 500 mg at the numeric rating scale of >4 which was assessed every 2nd hourly after shifting the patient to the post-operative ward. The time of shifting the patient to the post-operative ward was recorded as 0 h for pain assessment by numeric rating scale and time of administration of rescue analgesia was noted.

Assessment of motor blockade was carried out by the same observer at each minute till complete motor blockade occurs after drug injection.

Motor blockade was determined according to a modified bromage scale for upper extremities on a 3-point scale.

All patients were observed for any side effects such as nausea, vomiting, dryness of mouth, and complications such as pneumothorax, hematoma, local anesthetic toxicity, and post-block neuropathy in the intra and post-operative periods.

Statistical Data

At the end of the study, all the data are statistically analyzed using GRAPH PAD SOFTWARE quick calcs and VASSARSTATS.

- *P*-value was considered significant if <0.05 and highly significant if <0.001.

OBSERVATIONS AND RESULTS

Age, weight, height, and sex distribution was statistically analyzed using Fisher's exact test and $P = 0.30$ (>0.05) which is statistically insignificant.

Comparison of Onset of Sensory Block

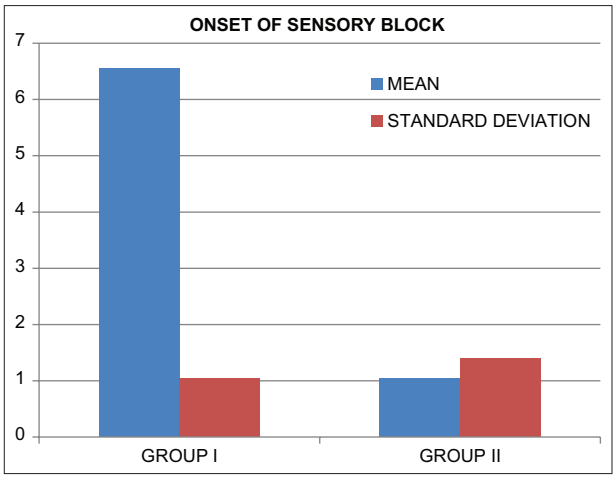
It was taken as the period from the time of injection of the anesthetic solution to the absence of pin prick sensation as experienced by the patient. (in minutes). Assessment of sensory block was done at each minute after completion of drug injection.

Time in minutes	Group I	Group II
Mean	6.57	6.87
Standard Deviation	1.05	1.40

$P = 0.2288$ which is not statistically significant. In both the groups, the mean onset time of sensory blockade was between, 6.56 and 6.86 min $P = 0.22$ which is statistically insignificant.

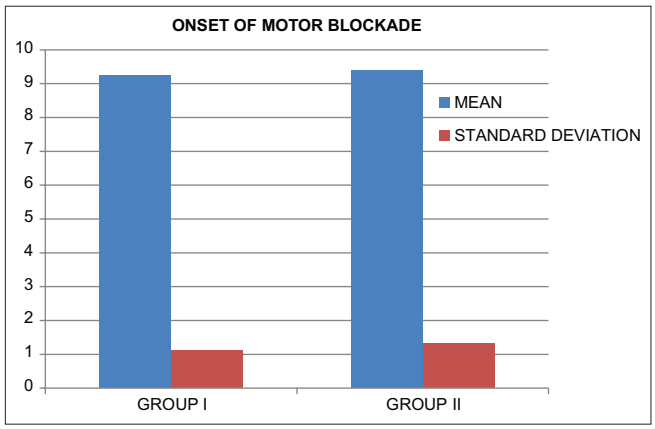
Comparison of Onset of Motor Blockade

It was considered when there was decreased motor strength with the ability to move fingers only. Assessment of motor block was carried out at each minute after completion



of drug injection by modified bromage scale for upper extremities on a 3 min scale.

Time in minutes	Group I	Group II
Mean	9.25	9.40
Standard deviation	1.10	1.31



$P = 0.56$ value which is not clinically significant. In both the groups, the onset of motor block was between 8 and 12 min.

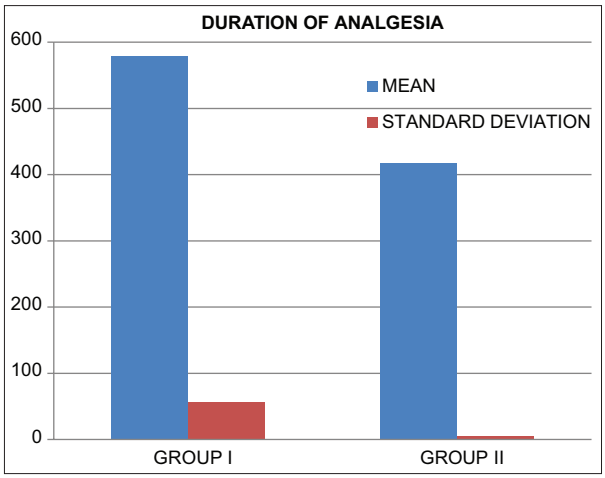
Comparison of Duration of Analgesia

It was taken as the time interval between the end of local anesthetic administration and the onset of pain and demand for rescue analgesia which was assessed using numerical rating scale of 0–10; recorded postoperatively every 2nd hourly till the score of 5.

Time in minutes	Group I	Group II
Mean	579.30	417.20
Standard Deviation	56.91	28.73

$P = 0.0001$ ($P < 0.05$).

The average duration of analgesia in Group I was 580 min which was significantly greater than the average duration of



analgesia of 420 min in Group II with $P < 0.0001$ indicating that the duration of analgesia is significantly prolonged in Group I when compared to Group II patients.

After shifting the patient to post-operative ward, the pain scores of the patient were assessed every 2nd hourly by numerical rating scale for pain assessment 0–10. The time of shifting the patient to post-operative ward was taken as 0 h and assessed.

The results were, up to 2 h postoperatively none of the patients in both the groups complained of pain. By 4th h, mild pain was complained in Group II with NRSP <5 which does not require any rescue analgesia but the pain was statistically significant when compared to Group I where no patient complained pain.

By the end of 6th h, there was significant pain complained by Group II that required administration of rescue analgesia where was as in Group I, only mild pain was complained.

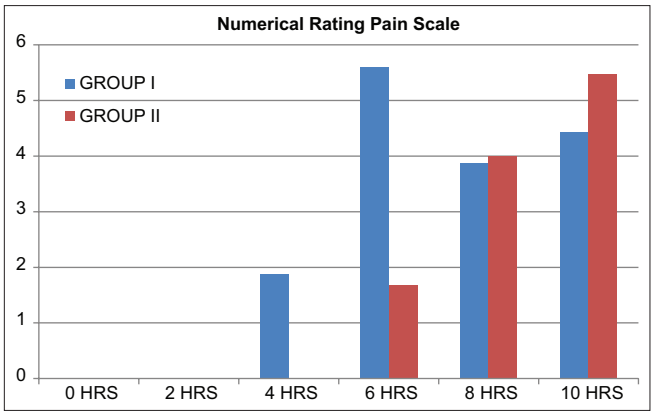
By the end of 8th h, mean pain scores were comparable between the two groups where Group I had pain score of <5 and Group II had decreased pain scores because of rescue analgesia administration.

By the end of 10th h, significant pain compliant started in Group I with mean pain scores of 5.48 which required administration of first rescue analgesia where as in Group II due to administration of rescue analgesia earlier the mean pain scores were <5.

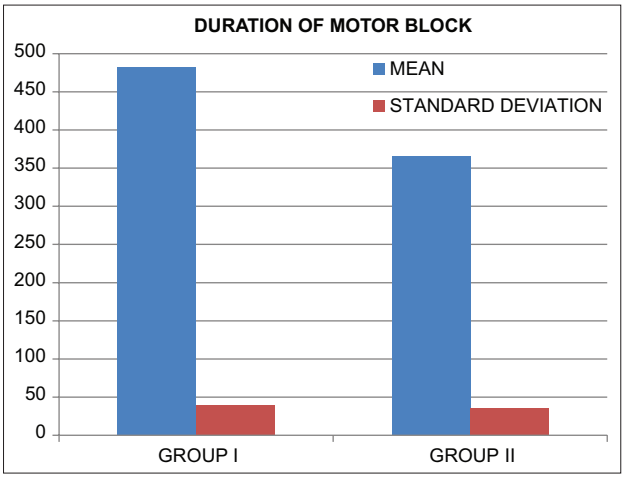
Duration of Motor Block

The duration of motor block was taken as the time interval between the end of local anesthetic administration and recovery of complete motor function of the hand and forearm.

$P < 0.0001$ (<0.05)



Time in minutes	Group I	Group II
Mean	481.70	365.10
Standard Deviation	39.00	35.04

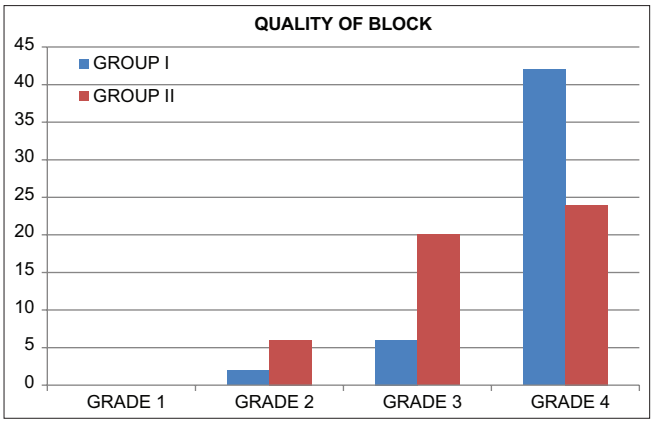


The average duration of motor block in Group I was 480 min which was significantly greater than the average duration of motor block of 365 min in Group II with $P < 0.0001$ indicating that the duration of analgesia is significantly prolonged in Group I when compared to Group II patients

Comparison of Quality of Block

	Group I	Group II
Grade 1	0	0
Grade 2	2 (4%)	6 (12%)
Grade 3	6 (12%)	20 (40%)
Grade 4	42 (84%)	24 (48%)

In Group I, 84% of patients achieved Grade 4 quality of blockade as opposed to 48% in Group II. Fischer's exact test was applied for assessment of quality of block with $P = 0.0005$ ($P < 0.05$) which was statistically significant, indicating that the quality of block was superior in Group I when compared to Group II. No patient had failed block



and 4% of patients in Group I and 12% of patients in Group II had Grade 2 block and 6(12%) of patients in Group I and 20 (40%) patients in Group II had Grade 3 block.

Comparison of Hemodynamic Parameters

The basal hemodynamic parameters were recorded initially and after drug administration every 15 min till 1 h and every 30 min until 180 min were recorded and compared. Pulse rate, systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure were statically insignificant.

The side effects in our study compared are nausea, vomiting, and dry mouth, about 60% of the patients have no side effects in both groups and the side effects are also minimal and were comparable in both the groups.

Complications such as hemothorax, pneumothorax, convulsions local anesthetic toxicity were not observed in any patients of in the present study groups.

DISCUSSION

The present study was designed to evaluate the efficacy of 0.75% ropivacaine with dexamethasone compared to 0.75% ropivacaine in ultrasound-guided supraclavicular brachial plexus block in patients undergoing upper limb surgeries.

Onset of Sensory Block

In the present study, it is observed that the onset of sensory block had mean duration of 6.56 ± 1.05 min in Group I and had mean duration 6.86 ± 1.40 min in Group II with $P = 0.22$ ($P > 0.05$).

The time for onset of sensory block is reduced in Group I than Group II, it is comparable because as $P = 0.22$ (>0.05) which was shown statistically insignificant.

The present study correlates to the study conducted by Pathak *et al*.,[1] who studied the effect of supraclavicular brachial plexus block with and without Dexamethasone – a comparative study, 50 patients were studied with two groups and conclude that the mean onset of sensory block in minutes was 5.92 ± 2.827 in dexamethasone group and 6.6 ± 2.958 in control group ($P = 0.4101$). Data were not significant statistically as $P > 0.05$. The onset of sensory blockade time with dexamethasone correlates with the present study.

Onset of Motor Blockade

In the present study, it is observed that the onset of motor block had a mean duration of 9.24 ± 1.10 min in Group I and had a mean duration of 9.38 ± 1.31 min in Group II and $P = 0.56$ ($P > 0.05$).

The time to onset of motor blockade is comparable in both the groups are comparable as P value is more than 0.05.

The present study was correlated with the study conducted by Shaikh *et al*.[2] Role of dexamethasone in Supraclavicular Brachial Plexus Block 60 patients studied with two groups. The onset time of motor block 19.96 ± 1.28 min in dexamethasone group versus 20.26 ± 1.28 min in control group) was also similar in the two groups ($P = 0.402$).

Duration of Analgesia

In the present study, it is observed that the duration of analgesia in Group I had a mean duration of 579.30 ± 56.91 (9.6 h) min and the mean duration of was 417.20 ± 28.73-min (6.95 h) in Group II and $P < 0.0001$ ($P < 0.05$) which is considered statistically significant.

There was a significant increase in duration of analgesia in dexamethasone group than control group and the difference was shown statistically significant.

The present study correlates with study done by, Dar and Jan.[3] The duration of pain relief (post-operative analgesia) was markedly prolonged in Group RD (14.5 ± 0.3 h), while it was only 8.3 ± 0.4 h in group R ($P < 0.001$). Which was statistically significant and showed that addition of dexamethasone to ropivacaine in supraclavicular brachial plexus block significantly prolongs the duration of analgesia and motor block in patients undergoing upper limb surgeries and is a remarkably safe and cost-effective method of providing post-operative analgesia.

This correlates well with the study conducted by Kalpana *et al*.[4] This study demonstrates that dexamethasone significantly prolongs the analgesic effect of plain ropivacaine 0.5% used as a single injection brachial plexus block. The mean time of onset of sensory block (13.85 ± 5.20 min) and motor block (22.17 ± 4.68 min) was significantly faster in Group D compared to Group R.

The present study results correlate with study conducted. In the year 2011, a study by Cummings *et al.*,[5] the mean duration of postoperative analgesia was around 22 h in a group which received ropivacaine with dexamethasone and it was around 11.8 h in group receiving ropivacaine only and stated that dexamethasone prolongs analgesia from interscalene blocks using ropivacaine or bupivacaine, with the effect being stronger with ropivacaine. However, block duration was longer with plain bupivacaine than ropivacaine. Thus, although dexamethasone prolonged the action of ropivacaine more than that of bupivacaine, the combined effect of dexamethasone and either drug produced nearly the same 22 h of analgesia.

The present study correlates well with one such randomized and prospective trial was done by Shrestha *et al.*[6] In their study, 40 patients undergoing arm, forearm, and hand surgeries were randomly selected. The 40 patients were divided in two groups of 20 each. In Group I, a brachial plexus block was done with 40–50 mL of local anesthetic with 1:200,000 adrenaline and in the other group, the block was performed with the same amount of local anesthetic with dexamethasone. Prolonged duration of analgesia occurred (12.75 ± 5.33 h verses 3.16 ± 0.48 h; $P = 0.00$) in the dexamethasone group than in the other group and concluded that addition of dexamethasone to local anesthetic significantly prolongs the post-operative analgesia.

The present study correlates well with Desmet *et al.*[7] In their study, they found that both IV and perineural administration of dexamethasone to supraclavicular brachial plexus block equivalently prolonged the duration of analgesia.

Duration of Motor Blockade

In the present study, it is observed that the duration of motor blockade in Group I had a mean duration of 481.70 ± 39.00 min and had a mean duration of 365.10 ± 35.04 min in Group II and $P < 0.0001$ ($P < 0.05$) which is considered statistically significant.

There was a significant increase in duration of motor blockade in dexamethasone group than control group and the difference was shown statistically significant.

The present study results correlate with study conducted by Movafegh *et al.*,[8] did a prospective, randomized, and double-blind study to evaluate the effect of dexamethasone added to lidocaine on the onset and duration of axillary brachial plexus block. Sixty patients scheduled for elective hand and forearm surgery under axillary brachial plexus block were randomly allocated to receive either 34 mL lidocaine 1.5% with 2 mL of isotonic saline chloride (control group, $n = 30$) or 34 mL lidocaine 1.5% with 2 mL of dexamethasone (8 mg) (dexamethasone group, $n = 30$). Neither epinephrine nor bicarbonate was added to the treatment mixture. They used a nerve stimulator in all of the patients. They found that the duration of surgery and the onset times of sensory and motor block were similar in the two groups. The duration of sensory (242 ± 76 vs. 98 ± 33 min) and motor (310 ± 81 vs. 130 ± 31 min) blockade were significantly longer in the dexamethasone than in the control group ($P < 0.01$)

The present study correlates well with One such study conducted by Shaikh *et al.*[2] The duration of motor block (846.67 ± 102.09 min in dexamethasone group versus 544.07 ± 55.40 min in control group) was also significantly longer in the dexamethasone group than in the control group ($P < 0.001$). Conclude that addition of 8 mg dexamethasone to bupivacaine 0.25% solution in supraclavicular brachial plexus block prolongs the duration of sensory and motor blockade, reduces the requirement of rescue analgesic in post-operative period but has no effect on the onset time of sensory and motor blockade.

Quality of Blockade

The quality of block was assessed by numeric rating scale from Grade I to Grade IV.

In the present study, it is observed that 84% (42/50) of the patients in Group I had Grade IV block when compared to 48% (24/50) in Group II with $P = 0.0005$ (<0.05) which is considered significant. The grades of quality of block in both the groups were already discussed in the table in our results.

The present study results correlate with study, this correlates well with the study conducted by Kalpana *et al.*[4] This study demonstrates that dexamethasone with ropivacaine and plain ropivacaine groups both were comparable in quality of blockade.

SUMMARY

In the present study, 60 patients of ASA I and ASA II of both sexes age between 18 and 50 years scheduled for elective upper limb surgeries and were randomly divided into two groups 30 each.

The two groups were designated as GROUP I and GROUP II

- Group I – 20 mL of 0.75% ropivacaine plus 2 mL of dexamethasone.
- Group II – 20 mL of 0.75% ropivacaine plus 2 mL of normal saline.

Parameters observed include onset of sensory blockade and motor blockade, duration of motor blockade, duration of analgesia (time to first request for analgesic), and quality of block.

- Onset of sensory and motor block was comparable in both the groups, which was shown statistically insignificant.
- The duration of analgesia in dexamethasone group was significantly prolonged as compared with control group and difference was statistically significant.
- The duration of motor block in dexamethasone group was significantly prolonged as compared with control group and difference was statistically significant.
- In dexamethasone group, there was enhanced quality of block with 88% achieved Grade IV block when compared to 52% in Group II which was statistically significant.
- The hemodynamic parameters, side effects, and complications were comparable in both the groups without any significant difference.

CONCLUSION

That Group I (addition of dexamethasone group) prolongs the motor block and enhances the quality of block and duration of analgesia significantly when compared with control group (normal saline) in supraclavicular brachial plexus block.

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Original Article

Does Substance Use Affect Electroconvulsive Therapy Outcome in Schizophrenia – Cohort and Descriptive Study

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Abstract

Introduction: Electroconvulsive therapy (ECT) has been used to treat schizophrenia, a chronic mental disorder characterized by symptoms such as delusions, hallucinations, disordered thinking, and abnormal behavior. This study aims to investigate the impact of substance abuse on ECT in patients with schizophrenia.

Methods: This prospective and cohort study was conducted at the Institute of Mental Health in Chennai over 1 year, with ethical committee approval. The study collected sociodemographic details such as age, gender, and others. The history of substance use was also documented, including information on the type of substances used. The baseline condition of the psychiatric illness of each patient was assessed using the brief psychiatry rating scale (BPRS) to determine the severity of symptoms.

Results: The study participants had an average age of 34.83 years with a standard deviation of 11.46. About 57.5% of them had a history of new substance use. The study's results showed a statistically significant difference in BPRS scores among patients who used cannabis, alcohol, nicotine, and tobacco before and after ECT. The BPRS scores for patients who used cannabis decreased from 52.71 ± 6.77 to 37.14 ± 10.27, and for alcohol, decreased from 50.78 ± 10.61 to 37.39 ± 11.19. For nicotine decreased from 51.00 ± 10.06 to 36.44 ± 10.73 and for tobacco decreased from 48.00 ± 11.28 to 37.58 ± 11.07.

Conclusion: It is important to note that the frequency and length of substance use determine the relationship between substance abuse and ECT treatment outcomes for schizophrenia patients.

Key words: Brief psychiatry rating scale, Electroconvulsive therapy, Schizophrenia, Substance use

INTRODUCTION

Psychiatric disorders like schizophrenia, affecting people of all backgrounds and socioeconomic statuses, are considered among the most debilitating worldwide.[1,2] In the world, 1% of the population suffers from schizophrenia. Electroconvulsive therapy (ECT), also known as ECT, was introduced in 1938 and used in psychiatry for over 75 years. After the introduction of psychotropic medications in the 1950s, their use declined but has increased in recent years. Due to the limited success of pharmacological treatments in some patients with depression and schizophrenia.[3-5] ECT is considered acceptable for major depression and is effective and safe, based on well-established research. According to some studies, up to 30% of patients with schizophrenia do not respond adequately to antipsychotic medication and experience persistent symptoms.[6,7]

The Epidemiological Catchment Area study found that a high proportion of patients with schizophrenia have issues with substance abuse compared to the general population. Specifically, 47% of patients with schizophrenia have reported severe problems with drug or alcohol use at some point in their lifetime, while only 16% of the general population has reported similar issues. According to the Epidemiological Catchment Area study,

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47% of patients with schizophrenia have severe problems with drug or alcohol use during their lifetime, compared to only 16% of the general population.[8,9] According to several studies, between 60% and 90% of patients with schizophrenia are said to have smoked cigarettes at some point in their lives. The estimated lifetime prevalence range for alcohol use disorders is 21–86%. According to reports, the lifetime prevalence of cannabis use ranges from 17% to 83%, and that of cocaine use is between 15% and 50%.[10-15]

Genetic risk factors for schizophrenia, particularly those related to neural systems that contribute to psychosis and addiction, can make patients more susceptible to substance abuse. The "primary addiction hypothesis" suggests that the susceptibility to schizophrenia primes the reward circuits in the brain, increasing the risk of drug addiction after exposure to drugs. The "two-hit hypothesis" suggests that drug abuse combined with other genetic and environmental risk factors can contribute to the development of schizophrenia. These hypotheses highlight the complex relationship between substance abuse and schizophrenia.[16] This study aims to investigate substance abuse's impact on ECT in patients with schizophrenia. Substance abuse can complicate the treatment of schizophrenia and may affect the effectiveness of ECT. Examining the effect of substance abuse on ECT parameters may provide valuable information for improving the treatment of schizophrenia and addressing substance abuse.

METHODS

This prospective and cohort study was conducted at the Institute of Mental Health in Chennai over 1 year, with ethical committee approval. The study included 40 male patients between 18 and 60 diagnosed with schizophrenia based on the ICD-10 criteria and was indicated for ECT treatment. Patients were included in the study through consecutive sampling and were willing to consent.

Patients with associated intellectual disabilities and those with psychiatric illnesses other than schizophrenia were excluded from the study.

The aim of the study was to compare the brief psychiatry rating scale (BPRS) scores of patients before and after ECT treatment, with a calculated standard deviation of 1.17, 80% power, and 95% confidence level.

The study collected sociodemographic details such as age, gender, and others. The history of substance use was also documented, including information on the type of substances used. The baseline condition of the psychiatric illness of each patient was assessed using the BPRS to determine the severity of symptoms. This information is important in understanding the relationship between substance abuse and the effectiveness of ECT in treating schizophrenia.

Table 1: Distribution of substance use among the study participants (*n*=40)

Distribution of each substance use	Number of patients (%)
Alcohol	18 (45)
Cannabis	7 (17.50)
Nicotine	16 (40)
Tobacco	12 (30)

Descriptive statistics were reported as mean (SD) for continuous variables and frequencies (percentage) for categorical variables. Chi-square at a 5% level of significance was used to find statistical significance. Fischer's exact test is when the expected cell count is <5. Repeated measure ANOVA was used to find the significant difference between time points. Data were statistically evaluated with IBM SPSS Statistics for Windows, Version 20.0.

RESULTS

The total mean age of the study participants was 34.83 ± 11.46 years. Around 57.5% had new substance use. Among the 40 patients, 18 (45%) had a history of alcohol use, and 7 (17.5%) patients had a history of cannabis use. Sixteen (40%) patients had a history of nicotine use, and 12 (30%) had a history of tobacco use [Table 1].

Among the study subjects, there were about 45% (n = 18) between 19 and 30 years, 17.5% (n = 7) between 31 and 40 years, 30% (n = 12) between 41 and 50 years, and 7.5% (n = 3) between 51 and 60 years.

Among alcohol users, the majority were in 19–30 years (55.6%), followed by 16.7% in both 31–40 years and 41–50 years, and 11.1% in 51–60 years.

Among cannabis users, the majority were in the age group of 19–30 years (71.4%) followed by 14.3% in 31–40 years and 51–60 years.

Among nicotine users, majority were in 19–30 years (37.5%) followed by 31.5% in 41–50 years, 18.8% in 31–40 years and 12.5% in 51–60 years.

Among tobacco users, majority were in 19–30 years (58.3%), followed by 25% in 41–50 years, 8.3% in 31–40 years and 51–60 years, respectively [Table 2].

A repeated measures ANOVA with a Greenhouse-Geisser correction determined that mean BPRS differed statistically significantly among alcohol users between time points (F [1.818, 30.912] = 76.111, $P < 0.001$). *Post hoc* analysis with a Bonferroni adjustment revealed that BPRS was statistically significantly decreased from pre-ECT to post-ECT (13.389 [95% CI, 9.69–17.08], $P \leq 0.001$), and from pre-ECT to on termination (26.056 (95% CI, 21.17–30.94), $P \leq 0.001$).

A repeated measures ANOVA with a Greenhouse-Geisser correction determined that the mean BPRS score differed significantly among cannabis users between time points (F [1.867, 11.199] = 43.425, $P < 0.001$), meaning that the mean BPRS score changed over time and the changes were statistically significant.

Post hoc analysis with a Bonferroni adjustment was conducted to investigate the differences between time points further. The study revealed that the mean BPRS score was statistically significantly decreased from pre-ECT to post-ECT (15.571 [95% CI, 7.44–23.70], $P \leq 0.003$), and from pre-ECT to on termination (27.71 [95% CI, 21.26–34.16], $P \leq 0.001$).

BPRS differed statistically significantly among nicotine users between time points (F [1.648, 24.473] = 80.54, $P < 0.001$). *Post hoc* analysis with a Bonferroni adjustment revealed that BPRS was statistically significantly decreased from pre-ECT to post-ECT (14.56 [95% CI, 11.24–17.88], $P \leq 0.003$), and from pre-ECT to on termination (26.94 [95% CI, 21.86–32.01], $P \leq 0.001$).

BPRS differed statistically significantly among tobacco users between time points (F [1.653, 18.18] = 47.69, $P < 0.001$). *Post hoc* analysis with a Bonferroni adjustment revealed that BPRS was statistically significantly decreased from pre-ECT to post-ECT (10.41 [95% CI, 6.43–14.40], $P \leq 0.001$), and from pre-ECT to on termination (23.58 [95% CI, 17.43–29.73], $P \leq 0.001$) [Table 3].

Table 2: Distribution of age among substance abuse

Age	Alcohol (%)	Cannabis (%)	Nicotine (%)	Tobacco (%)
19–30	10 (55.6)	5 (71.4)	6 (37.5)	7 (58.3)
31–40	3 (16.7)	1 (14.3)	3 (18.8)	1 (8.3)
41–50	3 (16.7)	0	5 (31.5)	3 (25)
51–60	2 (11.1)	1 (14.3)	2 (12.5)	1 (8.3)

Table 3: Distribution of BPRS pre- and post-electroconvulsive therapy among the substance use

Substance use	Mean±SD	95% CI	*P*-value
Alcohol			
Pre-ECT	50.78±10.619	45.497–56.059	-
Post-ETC	37.39±11.194	31.822–42.956	<0.001
On termination	24.72±5.278	22.097–27.347	<0.001
Cannabis			
Pre-ECT	52.71±6.77	46.448–58.980	-
Post-ETC	37.14±10.27	27.645–46.641	0.003
On termination	25.00±4.16	21.150–28.850	<0.001
Nicotine			
Pre-ECT	51.00±10.06	45.636–56.364	-
Post-ETC	36.44±10.73	30.718–42.157	<0.001
On termination	24.06±5.18	21.301–26.824	<0.001
Tobacco			
Pre-ECT	48.00±11.282	40.832–55.168	-
Post-ETC	37.58±11.07	30.547–44.619	<0.001
On termination	24.42±6.03	20.581–28.252	<0.001

DISCUSSION

Mental illnesses like schizophrenia and substance abuse are common and debilitating conditions that frequently coexist in the same person. Suicidal ideation and behavior are significantly increased in people with schizophrenia who abuse alcohol and other substances. The impact of alcohol on the brain is complex and influenced by multiple variables such as the amount consumed, age of first use, duration of use, personal characteristics, and health conditions.[16] In individuals with alcohol dependence, there is likely to be more significant brain damage than in those with alcohol abuse.

Research has shown that chronic alcoholics have a greater amount of brain shrinkage than healthy individuals, especially in brain regions such as the prefrontal cortex and limbic system, as seen in imaging studies and after-death examinations. Alcohol consumption can also lead to changes in neurotransmitters, particularly glutamate. Chronic alcohol use has been shown to increase the number of glutamate receptor sites in the hippocampus, which can become overstimulated and contribute to brain damage.[17]

In our findings, we have observed that BPRS was statistically significantly decreased from pre-ECT to post-ECT (13.389 [95% CI, 9.69–17.08], $P \leq 0.001$), and from pre-ECT to on termination (26.056 [95% CI, 21.17–30.94], $P \leq 0.001$). Our finding was consistent with the result of Moss *et al*., with no difference in ECT outcome between those with comorbid alcohol abuse and those without based on a percent decrease in pre- and post-ECT symptom scores (abuse: mean [SD], 0.89 [0.2] vs. non-abuse: mean [SD], 0.93 [0.16]; Wilcoxon, 1332; $P = 0.086$).[18] Cannabis use is prevalent among individuals

with schizophrenia and can have adverse effects on the course of the illness, including increased symptoms and decreased cognitive function.[19]

Smoking cigarettes has decreased serotonin levels in the brain and inhibiting monoamine oxidase. It leads to increased impulsivity and suicidality in individuals with mental health conditions such as schizoaffective disorder.[20] In the present study, we also found a significant decrease in BPRS scores in cannabis, nicotine, and tobacco users from pre-ECT to post-ECT. The accordance of a study conducted by Nicole *et al.* showed that adolescents and young adults who found positive for substance use had greater improvement in depression/functioning (-0.37 ± 0.14, $P = 0.009$), interpersonal relationships (-0.27 ± 0.13, $P = 0.045$), and emotional ability (-0.27 ± 0.14, $P = 0.044$) domains after the fifth ECT treatment.[21]

It is critical to have therapy that is both effective and safe. Including more detailed alcohol and drug histories, brain imaging, cognitive testing, and family histories of alcohol and drug abuse, as well as structured pre-treatment and post-therapy symptom assessments, could be included in the future studies. In summary, this study discovered that patients with schizophrenia who also had comorbid alcohol or substance abuse showed improvement after receiving ECT. The presence of alcohol dependence, nicotine dependence, tobacco usage, and cannabis dependence all impact the outcome; furthermore, this finding was found to be statistically significant in our study.

CONCLUSION

ECT is a highly effective treatment option for schizophrenia and substance abuse. The frequency with which patients use substances and the length of time that they have been sick before receiving ECT is important factors in determining the relationship between substance use and how well psychotic patients respond to ECT treatment. Further research is recommended to determine whether the duration of the current illness and the amount of substance use impact the effectiveness of ECT therapy in schizophrenia patients.

Limitations

The distinction between alcohol abuse and dependence is made through clinical assessment and examination, lacking objective measures of alcohol, and substance consumption at the time of the study. The impact of alcohol on the brain is diverse and subject to numerous variables such as the amount consumed, when it was first consumed, how long it was consumed, the individual's age, gender, family background, exposure to alcohol before birth, and any accompanying health conditions. Although complete information was not available in the study population, it is believed that individuals with alcohol dependence may have greater brain damage and dysfunction compared to those with alcohol abuse.

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Original Article

Antibiotic Sensitivity Pattern of Uropathogenic *Escherichia coli* in Pediatric Patients in a Tertiary Care Center in Kerala

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Abstract

Introduction: Urinary tract infections (UTI) are one of the most common but difficult to reliably diagnose clinically in children. The etiopathogenesis may range from urinary stasis due to improper toilet training or physical obstruction like phimosis to neural causes like neurogenic bladder or urogenital abnormalities. The most common uropathogen isolated is *Escherichia coli.* Prompt diagnosis and proper treatment as per the culture and sensitivity report are essential to avoid recurrent and chronic infections as well to prevent late complications like renal cortical scarring as a precedence to chronic renal failure.

Materials and Methods: The study was carried out in samples received from January 2022 to June 2022 to assess the antibiotic sensitivity pattern of Uropathogenic *E. coli* in pediatric patients and also to ascertain the prevalence of extended spectrum beta lactamase (ESBL) in these infections. Four hundred and thirty-two clean catch midstream urine samples were collected from pediatric patients during the study period and after exclusions, 129 samples of monobacterial growth of more than 100,000 cfu/mL were selected for the study. Out of these 129 g negative *bacterial* isolates, 78 isolates were identified as *E. coli*., these were subjected to disc diffusion based antibiotic sensitivity testing using the Kirby Bauer method and CLSI 2021 guidelines. Accordingly antibiotics Ampicillin (10 μg), Gentamicin (10 μg), Ciprofloxacin (5 μg), Levofloxacin (5 μg), Cotrimoxazole (25/1.25 μg), Amoxicillin-clavulanic acid (20/10 μg), Piperacillin/Tazobactum (100/10 μg), Norfloxacin (10 μg), Amikacin (30 μg), Ceftazidime (30 μg), Ceftazidime + clavulanic acid (20/10 μg), Cefuroxime (30 μg), Cefotaxime (30 μg), Imipenem (10 μg), Aztreonam (30 μg), Tetracycline (30 μg), Nitrofurantoin (300 μg), Tobramycin (10 μg), Colistin (10 μg), Etrapenem (10 μg), Doripenem (10 μg), and Meropenem (10 μg) were tested. Screening of ESBL producing *E. coli* was done with combined disc diffusion method using ceftazidime and ceftazidime-clavulanic acid in combination.

Results: Out of the 78 *E. coli* isolates, the screening for ESBL producers revealed that 50 isolates were ESBL positive. The antibiogram of 28 non-ESBL producers revealed that most isolates were resistant to Penicillins and cephalosporins. The non-ESBL producers showed sensitivity to Piperacillin-Tazobactum (100%), Carbapenems (100%), Nitrofurantoin (100%), Amikacin (96.4%), Ciprofloxacin (75%), Levofloxacin (78.5%), and Norfloxacin (75%). On the other hand, the ESBL producers were resistant to Penicillin, Beta lactams + inhibitors, Cephalosporins, Aminoglycosides, Tetracyclines, Folate pathway inhibitors, and Fluroquinolones.

Conclusion: UTI is a common health problem in children and is an important cause of morbidity and mortality. The effect of ESBL producers is very much evident in the sensitivity pattern wherein the Amoxycillin-Clavulanic acid reduces from 71.4% to 0% among ESBL producers. In the same way, Piperacillin-Tazobactum reduces from 100% to 52%, Amikacin reduces from 96.4% to 64%, and cephalosporins become totally ineffective in the ESBL producing strains. Every healthcare institution must develop its own antimicrobial treatment policy based on the culture and sensitivity report prevailing in the past 6 months. As per the antimicrobial stewardship programs in health-care facilities in low-and middle-income countries advised by the World Health Organization, these policies need to be reassessed at least once in 6 months to know the pattern of emerging resistance as well as to decide about the use of antibiotic recycling for the better usage of available antibiotics for the treatment of UTI.

Key words: AMR, Antibiotic resistance, *Escherichia coli*, Paediatric urinary tract infections, Renal scarring, Urinary tract infections, Uropathogenic *Escherichia coli*, Uropathogens

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INTRODUCTION

Urinary tract infections (UTI) are one of the most common infections in children. The infections can escalate very quickly to severe infections in the absence of a reliable history and non-specific examination findings. The prevalence varies with age. The prevalence of UTI is high in young infants, toddlers, and older adolescents. Female children are more commonly affected due to the shorter urethra and increased chance of *bacterial* entry from the gastrointestinal system due to anatomical proximity. In the same manner, uncircumcised male children also have a higher incidence of UTI due the higher *bacterial* skin flora concentration under the nappy in infancy as well as the surface area of foreskin which can act as a nidus for infection. As the infant grows up, toilet training, and voluntary holding, bladder stasis may act as factors predisposing the risk of UTI. Any condition that impairs the flow of urine or stasis may lead to development of UTI. These include neurogenic bladder, urogenital abnormalities, and altered immune function. These may lead to recurrent UTI leading to increase in hospital admissions and economic burden.[1]

REVIEW OF LITERATURE

UTI poses a major risk to growing children. If the UTI are not identified and treated properly, the developing renal cortex in children is vulnerable to renal scarring resulting in hypertension and chronic renal failure in later years of life.[2] As far as the data available from studies conducted in Kerala, the age group most affected by UTI is between 0 and 6 years.[3] The risk factors identified apart from the anatomical and pathological factors include uncircumcised boys, constipation, worm infestation, enuresis, wiping from back to front, and urethral instrumentation.[4] The most common *bacterial* involved in causation of UTI happens to be *Escherichia coli* followed by *Klebsiella*, Coagulase negative *Staphylococcus*, *Citrobacter*, *Enterococcus*, *Acinetobacter* spp, Proteus vulgaris, and *Staphylococcus aureus*.

Most common isolates of pediatric bacteriuria belong to the Gram-negative coliform group of *bacteria* which ascend the urinary tract. *E. coli* have specific properties like the fimbriae which help the *bacteria* attach to uroepithelial surface thereby allowing the *bacteria* to overcome host defenses easily.[5] Other factors that help in causation of urinary tract infection include α-hemolysin, M hemagglutinin, endotoxin, cytotoxic necrotizing factor 1, K capsular antigen, a rigid cell wall, serum resistance ability due to the outer membrane protein TraT, aerobactin which supports growth by chelating iron, and adhesive capacity. Upper urinary tract infection involves the kidneys and ureters.[6] The three different types of adhesins identified on uropathogenic *E. coli* include Type 1 pili (or fimbriae), Pfimbriae, and X-adhesins These adhesins facilitate adherence of the *bacteria* to mucosal receptors in the uroepithelium in spite of the flushing action of urine flow.[7,8] Once the uroepithelium is invaded, an intracellular biofilm is formed.[7] The biofilm can protect the uropathogenic *E. coli* from the host immune system. The patients with upper urinary tract infection present with abdominal pain, loin tenderness along with fever, anorexia, vomiting, lethargy, and malaise. Lower urinary tract involves the bladder and urethra and thus the symptoms are more localized like lower abdominal pain, dysuria, urinary frequency, and urgency. In younger patients, the classical signs are absent and thus the differentiation between upper and lower UTI becomes less obvious.[9] The clinical symptoms may vary from mild dysuria to life-threatening urosepsis. Fortunately, severe infections are less common and if they do occur, they are more commonly seen in neonates.[9-11] UTI is more common cause of occult infections in infants. Pediatric population can also become victims of short-term morbidity with poor oral intake and dehydration apart from the rare case cases of perinephric abscess formation. In some cases, the spread of uropathogens can occur through the hematogenous route as well. Meningitis can also occur with hematogenous spread to cerebrospinal fluid and is more predominant in infants.

Long-term morbidity can occur following UTI. It has been documented that 15% of children will have evidence of renal scarring following single incidence of urinary tract infection. This scarring becomes important if it leads to renal dysfunction, hypertension, and chronic kidney disease (CKD).[12] In the absence of renal abnormalities or recurrent UTI, the risk of CKD is seen to be minimal.[13] There is a genetic predisposition to recurrent UTI and renal scarring. Genes that have been shown to predispose patients to recurrent UTI and renal scarring include angiotensin-converting enzyme insertion/deletion gene, Interleukin (IL)-8 receptor CXCR1 and CXCR2 genes, IL-10-1082 A/G gene, heat shock protein 72 gene, transforming growth factor-β1 gene, toll-like receptor pathway genes, and vascular endothelial growth factor gene.[14-19]

In view of the above-mentioned morbidity and long-term complications, effective diagnosis and treatment of UTI gain importance. As far as the diagnosis is concerned, there are challenges as the pediatric age patients cannot explain the symptoms and is based on the observation of the parent and good clinical examination. The next challenge comes with sample collection and it is very difficult to obtain a clean catch midstream urine sample (CCMSU). The urinary screening with microscopy or dip stick methods is not effective in ascertaining the diagnosis of UTI. In the given scenario, it is imperative for every healthcare institution to develop an antibiotic policy based on the culture and

sensitivity pattern so that an effective empiric therapy can be instituted in cases of pediatric UTI.

MATERIALS AND METHODS

The study was conducted at Azeezia institute of Medical Sciences and Research, Kollam district of Kerala State during the period of January 2022–June 2022 to assess the antibiotic sensitivity pattern of uropathogenic *E. coli* among the isolates from urinary samples of pediatric patients reporting to the pediatric department hospital with complaints or signs and symptoms suggestive of UTI.

All non-repetitive midstream urine samples obtained during the study period were included in the study. A total of 432 CCMSU samples were received in the microbiology laboratory during the study period. These samples were subjected to wet mount examination and were inoculated to 5% sheep blood agar and MacConkey agar plates. The plates were kept for incubation at 37°C for 18–24 h. After 24 h of incubation at 37°C 255, samples did not show any evidence of *bacterial* growth and were reported as No Growth. Twenty-eight samples showed presence of more than three types of *bacterial* growth which also corroborated with the wet mount findings and were not processed further. After exclusions, totally 149 samples of monobacterial growth of more than 10^5cfu/mL were considered for the study. Twenty samples grew Gram-positive organisms such as *S. aureus, Staphylococcus epidermidis, Streptococcus* spp., and *Enterococcus* spp. One hundred and twenty-nine isolates were Gram-negative *bacilli* out of which 51 isolates were *Klebsiella pneumoniae* and remaining were *Citrobacter* spp., *Enterobacter*, *Proteus vulgaris*, *Proteus mirabilis*, *Pseudomonas aeruginosa,* and *Acinetobacter* spp. Seventy-eight isolates were *E. coli* and these isolates were considered for the present study.

Processing of Samples

All samples were cultured on culture enriched and selective media by semi-quantitative method. Samples were inoculated on 5% sheep blood agar plate and Mac Conkey agar plate by streaking using sterile calibrated wire loop and incubated aerobically for 18–24 h at 37°C. Samples which showed monobacterial significant grown (>10^5 CFU/mL) were included in this study. Isolation and identification of isolates were based on their morphology in gram staining, cultural characteristics, and biochemical reactions.[20] Antibiotic susceptibility testing of all isolates was performed by Kirby–Bauer's disc diffusion method and interpretation of the results was done based on CLSI 2021. *Bacterial* suspension was made and compared to 0.5 McFarland turbidity standards in peptone water. Antibiotic discs (Himedia Laboratories Pvt. Ltd. Mumbai) used were Ampicillin (10 μg), Gentamicin (10 μg), Ciprofloxacin (5 μg), Levofloxacin (5 μg), Cotrimoxazole (25/1.25 μg), Amoxicillin-clavulanic acid (20/10 μg), Piperacillin/Tazobactum (100/10 μg), Norfloxacin (10 μg), Amikacin (30 μg), Ceftazidime (30 μg), Ceftazidime + clavulanic acid (20/10 μg), Cefuroxime (30 μg), Cefotaxime (30 μg), Imipenem (10 μg), Aztreonam (30 μg), Tetracycline (30 μg), Nitrofurantoin (300 μg), Tobramycin (10 μg), Colistin (10 μg), Etrapenem (10 μg), Doripenem (10 μg), and Meropenem (10 μg).

Procedure

Antibiotic sensitivity testing was done using Kirby-Bauer method. Discs were applied aseptically. Gap of 24 mm centre-centre was ensured as per CLSI guidelines. Plates were Incubated at 35 ± 2°C and examined after a minimum of 16–18 h.

Screening for Extended Spectrum Beta Lactamase (ESBL) Isolates

Screening of ESBL producing *E. coli* according to CLSI guidelines, strains showing zone of inhibition of ≤22 mm for Ceftazidime and/or ≤17 mm for Cefpodoxime and/or ≤27 mm for Cefotaxime were considered for confirmation test for ESBL. ESBL producing *E. coli* isolates were the sub-cultured into sterile nutrient agar plates and incubated for 24–48 h. The isolated single colonies were used for further comparative studies. ESBL production among potential ESBL producing isolates was confirmed phenotypically using combined disc diffusion method. Comparison of the zone of inhibition was made for the Ceftazidime (30 μg) versus that of the Ceftazidime disc in combination with clavulanic acid (30/10 μg), placed 25 mm apart (center to center). A difference in the inhibition zone diameter of ≥5 mm for a combination disc versus ceftazidime disc alone confirmed ESBL production (Phenotypic Confirmatory Disc Diffusion Test).[21]

RESULTS

Out of the 78 *E. coli* isolates, the screening for ESBL producers revealed that 50 isolates were ESBL positive. The antibiogram of 28 non-ESBL producers revealed that most isolates were resistant to penicillins and cephalosporins. The non-ESBL producers showed sensitivity to Piperacillin-Tazobactum (100%), Carbapenems (100%), Nitrofurantoin (100%), Amikacin (96.4%), Ciprofloxacin (75%), Levofloxacin (78.5%), and Norfloxacin (75%). On the other hand, the ESBL producers were resistant to Penicillin, Beta lactams + inhibitors, Cephalosporins, Aminoglycosides, Tetracyclines, Folate pathway inhibitors, and Fluroquinolones [Table 1].

DISCUSSION

UTI is a common health problem in children and is an important cause of morbidity and mortality. *Bacteria* play a major role in these infections and among the *bacteria,* Gram-negative organisms like *E. coli* are the most common uropathogens causing infections. The anatomical factors play a major role in causation of infection whereby the *bacteria* in the gastrointestinal tract find an easy way to enter into the renal system and cause infection assisted by the virulence factors present in the *bacteria*. The issues involving the diagnosis of pediatric UTI include non-reporting of symptoms by preverbal children. Parents may notice lethargy, irritability, poor feeding, and vomiting. Fever may or may not be present. The change in odor or color of urine may be missed in nappy wearing children. Older children may be able to report clinical symptoms precisely and may be confirmed with clinical examination and culture using the CCMSU sample. In patients in whom the sample collection is doubtful may be subjected to invasive methods of sample collection including catheterized sample or using supra pubic aspiration of urine.

As the chances of renal injury and CKD is more in children, it is essential to treat *bacterial* urinary tract infection as per the local guidelines and sensitivity patterns as the susceptibility can vary significantly in different regions. In our study, out of the Gram-negative bacteriuria accounting to 129 isolates, 78 were *E. coli*. Among the *E. coli,* 28 isolates were non-ESBL producers and 50 were ESBL producers accounting to 64.1%. The implication of the increase in ESBL producers results in increased antibiotic drug resistance leading to clinical treatment failures and increased chances of reinfection and recurrent UTI. The effect of ESBL producers is very much evident in the sensitivity pattern wherein the Amoxycillin-Clavulanic acid reduces from 71.4% to 0% among ESBL producers. In the same way, Piperacillin-Tazobactum reduces from 100% to 52%, Amikacin reduces from 96.4% to 64% and cephalosporins become totally ineffective in the ESBL producing strains. The results in our study as well as the study conducted by Lok Bahadur Shrestha *et al*.[22] emphasize on the importance of screening for UTI with culture and sensitivity in pediatric infections.

Table 1: Comparison of antibiotic sensitivity of uropathogenic *Escherichia coli* isolates

Class	Antibiotics	*Escherichia coli*	ESBL *Escherichia coli*
		n=28	*n*=50
Penicillin	Ampicillin	35.7	0.0
β Lactam+Inhibitor	AMOX-CLAV	71.4	0.0
	PIP-TAZ	100	52.0
Cephalosporins II	Cefuroxime	39.2	0.0
III	Cefotaxime	35.7	0.0
	Ceftazidime	39.2	0.0
Carbapenams	Imipenam	100	72.0
	Meropenam	100	50.0
Aminoglycosides	Gentamicin	53.5	32.0
	Tobramycin	64.2	20.0
	Amikacin	96.4	64.0
Tetracyclins	Tetracycline	67.8	32.0
Fluroquinolones	Ciprofloxacin	75.0	44.0
	Levofloxacin	78.5	28.0
	Norfloxacin	75.0	42.0
Folate pathway (−)	Cotrimoxazole	53.5	48.0
Nitrofurans	Nitrofurantoin	100	86.0

Values mentioned are in percentages (%)

As per the Standard treatment guidelines issued by the Indian Academy of Pediatrics for the year 2022 has suggested Cefixime, Amoxicillin or co-amoxiclav, Cephalexin or Cefadroxil as oral antibiotics. In patients requiring parenteral antibiotics Amikacin, Gentamicin, Cefotaxime, or Ceftriaxone may be tried for UTI. As for those children requiring prophylaxis for prevention of UTI, Cotrimoxazole, Nitrofurantoin, Cephalexin, or Cefadroxil may be used.[23] However, in India, it would be ideal to rely on culture and sensitivity reports in view of higher antimicrobial resistance pattern, the markedly increasing ESBL produced among *Enterobacteriaceae*, the difficulties in reporting and diagnosis of UTI are to be considered. It is worthwhile to be noted that every healthcare institution must develop its own antimicrobial treatment policy based on the culture and sensitivity report prevailing in the past 6 months. As per the antimicrobial stewardship programs in health-care facilities in low- and middle- income countries advised by the World Health Organization, these policies need to be reassessed at least once in 6 months to know the pattern of emerging resistance as well as to decide about the use of antibiotic recycling for the better usage of available antibiotics for treatment of UTI.

CONCLUSION

Urinary Tract Infections is one of the most common infections in children and is an important cause of morbidity and mortality. The aetiology is multi-factorial and urinary culture & sensitivity testing is mandatory for identification of the uropathogen. In our study the effect of ESBL producers is very much evident in the sensitivity pattern wherein the Amoxycillin-Clavulanic acid reduces from 71.4% to 0% among ESBL producers. In the same way Piperacillin-Tazobactum reduces from 100% to 52%, Amikacin reduces from 96.4% to 64% and cephalosporins become totally ineffective in the ESBL producing strains. Every healthcare institution must develop its own antimicrobial treatment policy based on the culture and sensitivity report prevailing in the past six months. As per

the antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries advised by the World Health Organization these policies need to be reassessed at least once in six months to know the pattern of emerging resistance as well as to decide about the use of antibiotic recycling for the better usage of available antibiotics for treatment of UTI.

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Original Article

Comparative Study of Dexamethasone Addition to Granisetron and Palonosetron in Preventing Post-operative Nausea and Vomiting in Cesarean Section under Spinal Anaesthesia

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Abstract

Background: Post-operative nausea and vomiting (PONV) are defined as nausea and vomiting that occurs within 24 h after surgery done under general/regional/local anesthesia. Nausea and vomiting in the post-operative period occur in 20–30% of patients and together are the second most common symptom after pain. The present study was designed to compare addition of dexamethasone to granisetron and palonosetron in preventing PONV in cesarean section under spinal anesthesia.

Materials and Methods: This prospective, randomized, and double-blind study was carried on 100 parturients admitted in Government Medical College and associated Guru Nanak Dev Hospital, Amritsar, aged 20–35 years of ASA grade I and II scheduled for elective caesarean under spinal anesthesia. Aims and objective of this study was primarily to compare the effectiveness of dexamethasone to granisetron and palonosetron in preventing PONV in cesarean section under spinal anesthesia. The secondary aim of our study was hemodynamic monitoring and to see any side effects/complications related to the above drugs.

Results: The incidence of postoperative nausea, retching, and vomiting was less in group PD as compared to group GD during 0–24-h period but the difference came out to be statistically non-significant ($P > 0.05$). Hemodynamic parameters during pre-operative, intraoperative, and post-operative period were comparable. Incidence of bradycardia and hypotension in both groups was also comparable.

Conclusion: Although palonosetron is better than granisetron, the cost-effectiveness of granisetron makes it a more commonly used drug in a setting with a limited resources.

Key words: Dexamethasone, Granisetron, Palonosetron, Post-operative nausea vomiting

INTRODUCTION

Post-operative nausea and vomiting (PONV) is defined as nausea and vomiting that occurs within 24 h after surgery done under general/regional/local anesthesia. Nausea and vomiting in the post-operative period occurs in 20–30% of patients and together are the second most common symptom after pain.[1] Nausea is defined as a subjective unpleasant sensation associated with awareness of the urge to vomit, usually felt in the back of the throat and epigastrium and is accompanied by the loss of gastric tone and reflux of the duodenal contents into the stomach. Vomiting is defined as forceful expulsion of gastric contents from mouth and is brought out by the powerful sustained contraction of abdominal muscles, descent of diaphragm, and opening of gastric cardia. There are several factors attributing to nausea and vomiting in patients undergoing cesarean section such as pressure on stomach and gut, neural factors as vagal reflexes elicited by irritation of parasympathetic nerve endings in the abdomen. PONV can lead to delay in recovery time,

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prolonged nursing care, prolonged hospital stay, and increase in total health care costs.[2] Granisetron is a selective 5HT3 receptor antagonist, more potent, and has longer acting properties against cisplatin-induced emesis than ondansetron.[3] Palonosetron, a newer second generation 5HT3 antagonist has been approved by the United States Food and Drug Administration for prevention of PONV in 2008.[3] Dexamethasone (8 mg) decreases chemotherapy induced emesis when added to antiemetic regimen. The present study was conducted to compare to efficacy of dexamethasone addition to granisetron and palonosetron for prevention of PONV in patients undergoing cesarean section under spinal anesthesia.

MATERIALS AND METHODS

After institutional ethical committee approval and informed written consent from the participant, a prospective, randomized, and double-blind study was carried in Government Medical College and associated Guru Nanak Dev Hospital, Amritsar. Parturient aged 20–35 years of age and ASA Grade I and II scheduled for elective cesarean delivery under spinal anesthesia were included in the study. Patients with the previous history of subacute intestinal obstruction, hiatus hernia, previous gastric surgery, history of motion sickness, severe cardiac, respiratory, neurological diseases, and bleeding disorders were excluded from the study. Patients with medical history of pre-eclampsia, diabetes, placenta previa were also excluded from the study. All patients included in the study were examined in detail during pre-anesthetic checkup after taking fully informed consent in their vernacular language. Systemic Examination was done for respiratory system, cardiovascular system, and nervous system. All routine investigations were done. Patients were randomly divided into two groups of 50 each, that is, Group GD and Group PD. Each group received one of the following two drug regimens. Group GD (n = 50) received Inj. Granisetron 40 μg/kg and Inj. Dexamethasone 8 mg diluted in normal saline to make 5 mL given intravenously. Group PD (n = 50) received Inj. Palonosetron 1 μg/kg and inj. Dexamethasone 8 mg diluted in normal saline to make 5 mL given intravenously. On the day of surgery, all the vitals parameters were recorded preoperatively. After shifting the patient to the operation theatre, multiparameter monitor was attached to the patients and a continuous monitoring of pulse rate, blood pressure, respiratory rate, and SPO_2 was done. After venous cannulation, patient was preloaded with ringer lactate solution (15 mL/kg) before giving spinal anesthesia. Under all aseptic precautions, patient was made to lie in left decubitus position. Patient's back was painted with povidone iodine solution and drapped with sterile sheet, 2.2 mL of inj. bupivacaine 0.5% hyperbaric was injected slowly over 15 s through a 25 G spinal needle inserted in L3-L4 intervertebral space. Patient was shifted to supine position, with the left uterine displacement using a wedge under the right hip or 15° table tilt. If there was any difficulty in giving drug in L3-L4 space then L2- L3 intervertebral space was used but no head down tilt was given. Level of analgesia was assessed by pinprick method and surgery was allowed to start when T10 level was achieved. Oxygen was started at a rate of 5 L/min in all patients through facemask. Maternal bradycardia and hypotention were noted and prevented intraoperatively. Any episode of nausea and vomiting was noted during intraoperative period. The drugs under study were administered intravenously immediately after clamping the umbilical cord as discussed above. Any episode of nausea, retching, or vomiting was noted for 24 h in the post-operative period. Nausea is verbal rating scale where patients describe their symptoms as NAUSEA SCORE (No Nausea: 0; Mild Nausea: 1–3; Moderate Nausea: 4–6; and Severe Nausea: 7–10). Total number of episodes of vomiting were counted and those with two or more episodes of vomiting were given the rescue medication Inj. Metoclopramide 10 mg intravenous. Patients were shifted to recovery room where they were monitored postoperatively.

Statistical Analysis

After taking consultation with statisticians and monitoring parameters of the study, that is, nausea, retching, and vomiting, blood pressure, oxygen saturation, respiratory rate, pulse rate, pain score, adverse effects of the study drugs, etc. and to make the power of the study more than 85%, this study was conducted in 50 each. The data from the present study was systematically collected, compiled, and statistically analyzed to draw relevant conclusion. Sample size was calculated keeping in view at most 5% risk, with minimum 85% power and 5% significance level (significant at 95% confidence interval). Data were recorded in a Microsoft excel spread sheet and analyzed using Statistical Package for the IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp., Chicago. Continuous data were presented as mean with standard deviation. Categorical data were expressed as percentages. Numerical variables were normally distributed and were compared using Chi-square test for non-parametric data and independent "t"-test for parametric data. The P-value was then determined to evaluate the level of significance. The results were analyzed and compared to the previous studies to draw relevant conclusions.

OBSERVATION AND RESULTS

The mean age in groups GD and PD was 26.24 ± 3.32 and 25.50 ± 3.23 years respectively. In Group GD, the mean weight of patients was 62.52 ± 4.67 kg and in Group PD,

the mean weight was 62.12 ± 5.75 kg. In Group GD, 38 (76%) patients were of ASA grade I and 12 (24%) patients were of ASA grade II. In Group PD, 42 (84%) patients were of ASA grade I and 8 (16%) patients were of grade II. In Group GD, there were 10(20%) primipara patients and 40(80%) patients were multiparous. While in Group PD, there were 9 (18%) primipara patients and 41(82%) were multiparous patients. Hence, in relation to demographic profile, there was no significant difference between the two groups ($P > 0.05$) as in Table 1.

Post-operative nausea, retching, and vomiting were observed in 10%, 8%, and 6% of patients, respectively, in Group GD whereas only 6% of patients experienced nausea and 4% of patients were having retching and vomiting in Group PD during 0–6 h period. The same difference was maintained during 7–12 h and 13–24 h. Hence, the incidence of post-operative nausea, retching and vomiting was less in group PD as compared to Group GD during 0–24 h period but the difference came out to be statistically non-significant ($P > 0.05$) as in Table 2.

Out of 50 patients in each group, 6 (12%) patients required rescue antiemetic in group GD. Only 2 (4%) patient required rescue antiemetic in group PD during post-operative period. Requirement of rescue pain relief among the two groups was comparable. Group GD required rescue analgesic in 5 (10%) patients whereas Group PD required rescue analgesic in 3 (6%) patients as in Table 3.

Patient satisfaction score was generated with respect to satisfaction with the study drugs in both the groups. Patients having satisfaction score of 4 and 5 were taken as satisfied. Patients having satisfaction score of 1, 2, and 3 were taken as not satisfied. In Group GD, 40 (80%) patients were satisfied and in Group PD, 45 (90%) patients were satisfied. The difference among the two groups with regard to satisfaction of the patients was statistically non-significant ($P = 0.161$) as in Table 4.

Pulse rate, systolic and diastolic blood pressure, respiratory rate, and SPO2 were comparable at different time intervals during intraoperative (0–60 min) period. During post-operative period, the mean of hemodynamic parameters was taken at 0–6-h, 7–12-h, and 13–24-h period. Both the groups were found to be comparable. Variations were statistically insignificant ($P > 0.05$).

Table 1: Demographic profile

Parameter	Group GD (*n*=50)	Group PD (*n*=50)	*P*-value (NS)
Mean age (in years)	26.24±3.32	25.50±3.23	0.331
Weight	62.52±4.67	62.12±5.75	0.70
ASA status			0.317
I	38	42	
II	12	8	
Parity			
Primipara	10	9	0.414
Multipara	40	41	

DISCUSSION

PONV is one of the most common post-operative problem in anesthesia and remains a challenge especially in obstetric population. The factors responsible for the increase in the incidence of PONV during cesarean section under

Table 2: Comparison of nausea, vomiting, and retching between two groups

Time (in hours)	GD		PD		χ^2 (df=1)	"*P*"-value	Remarks
	No.	%	No.	%			
0–6 h							
Nausea	5	10.00	3	6.00	0.543	0.461	NS
Mild	2	4.00	1	2.00			
Moderate	2	4.00	2	4.00			
Severe	1	2.00	0	0.00			
Retching	4	8.00	2	4.00	0.709	0.399	NS
Vomiting	3	6.00	2	4.00	0.211	0.645	NS
7–12 h							
Nausea	4	8.00	2	4.00	0.709	0.399	NS
Mild	2	4.00	1	2.00			
Moderate	2	4.00	1	2.00			
Severe	0	0.00	0	0.00			
Retching	3	6.00	2	4.00	0.211	0.654	NS
Vomiting	2	4.00	1	2.00	0.344	0.557	NS
13–24 h							
Nausea	1	2.00	0	0.00	0.010	0.314	NS
Mild	0	0.00	0	0.00			
Moderate	1	2.00	0	0.00			
Severe	0	0.00	0	0.00			
Retching	1	2.00	0	0.00	0.010	0.314	NS
Vomiting	1	2.00	0	0.00	0.010	0.314	NS

Table 3: Need for rescue antiemetic in both groups

Rescue antiemetic	Group GD		Group PD		χ^2	"*P*"- value
	No.	%	No.	%		
Given	6	12.00	2	4.00	2.174	0.140
Not given	44	88.00	48	96.00		
Total	50	100.00	50	100.00		

Table 4: Patient satisfication score

Patient satisfaction score	GD		PD		χ^2	"*P*"- value	Remarks
	No.	%	No.	%			
Satisfied (score 4,5)	40	80.00	45	90.00	1.961	0.161	NS
Not satisfied (score 1,2,3)	10	20.00	5	10.00			
Total	50	100.00	50	100.00			

spinal anesthesia are maternal demographics, operative procedures, anesthetic technique, post-operative pain, use of perioperative opioids, anxiety, hypotension, and hypoperfusion of the CNS, abrupt visceral movements, exteriorization of the uterus, traction of the peritoneun, increased intraabdominal pressure, hormonal changes, and use of uterotonic agents. PONV has several undesirable consequences such as delayed mother and baby bonding, delayed breast feeding, pulmonary aspiration of gastric contents, metabolic alkalosis, risk of bleeding and increased intraabdominal pressure causing suture line dehiscence, and incisional hernia. It can cause apprehension and anxiety in subsequent pregnancy. Hence, prevention of PONV is very important.

As pathophysiology of PONV is multifactorial so no single antiemetic drug can provide better prophylaxis. An ideal antiemetic should have quick onset, long duration of action, and minimal side effects. Hence, drugs with different mechanisms of action can be used in combination for better prophylaxis and less side effects of each drug.

In our study, the difference between the two groups was statistically insignificant when demographic parameters were compared, that is, age, weight, ASA grading, and parity.

In our study, when we compared the incidence of nausea between two groups at different time interval from 0 to 24-h period, we found that incidence of nausea was less in PD group as compared to GD group but the difference was statistically insignificant ($P > 0.05$). Our study results are in accordance with the study conducted by Chilana *et al*. in which they observed that incidence of nausea was 5% during 0–6 h period, 5% during 6–12 h period and 0% during 12–24 h period with granisetron + dexamethasone combination.[4] Similarly, a study conducted by Nagappa *et al*. reported 8.6% incidence of nausea during 0–4 h and 11.4% during 4–24 h in granisetron + dexamethasone group.[5] Another study was done by Khuo *et al*. where they found the incidence of nausea with palonosetron + dexamethasone combination was 5% during 0–6 h, 1.7% during 6–12 h, and 3.3% during 12–24 h period.[6]

In the present study, group GD, 3 (6%) patients had retching during 0–6 h period and 3(6%) patients during 7–12 h period had retching. During 13–24 h period, only 1(2%) patient had retching. In Group PD, 2 (4%) patients had retching during 0–6 h period and 2(4%) patients had retching during 7–12 h period. No patient had any episode of retching during 13–24 h period. Hence, we observed that the incidence of retching was less in Group PD as compared to Group GD but the difference was statistically non-significant ($P > 0.05$). Our results of retching were comparable with the study done by Bhattacharjee *et al*. as they also found less incidence of retching in palonosetron (3.3% in 0–3 h, 3.3% in 3–24 h) and granisetron (3.3% in 0–3 h and 3.3% in 3–24 h) groups.[7]

In our study, we found that incidence of vomiting was lower in PD group as compared to GD group but the difference was statistically non-significant ($P > 0.05$). In a study conducted by Khuo *et al*. where they found that the incidence of vomiting in palonosetron +dexamethasone group was 3.4% during 0–6 h period, 0% from 6 to 24 h period. The results of our study were in concordance with the above study.[6] Another study done by Chilana *et al*. where they found the incidence of vomting was 2.5% during 0–6 h period, 2.5% during 6–12 h period, and 0% during 7–12 h in granisetron +dexamethasone which were comparable with our study.[4]

In Group GD, 6 (12%) patients received rescue anti-emetic during post-operative period. In Group PD, only 2 (4%) patients were given rescue anti-emetic in the post-operative period. Although the number of patients requiring rescue anti-emetic in Group PD was less than group GD but the difference was statistically insignificant($P > 0.05$) which is in accordance with the study conducted by Kovac *et al*. in which they found that patients at high risk of PONV who received combination therapy required less rescue antiemetic. Hence, adding dexamethasone to granisetron and palonosetron decreases the requirement of rescue antiemetic medication.[8]

During post-operative period, the mean of hemodynamic parameters was taken at 0–6-h, 7–12-h, and 13–24-h period. Both the groups were found to be comparable and statistically insignificant ($P > 0.05$).Our results were in concordance with the study done by Tahir *et al*. as they also observed that hemodynamic parameters were comparable both during intraoperative and post-operative period at different time intervals.[9]

In Group GD, 40(80%) patients were satisfied and in Group PD 45(90%) patients were satisfied. The difference among the two groups with regard to satisfaction of the patients was statistically non-significant ($P = 0.161$).Our results were comparable to the study done by Srivastava *et al*. where they compared palonosetron + dexamethasone and ondansetron + dexamethasone for prevention of PONV in middle ear surgeries and found that the satisfaction score for the palonosetron + dexamethasone group was 90.31 ± 8.61% which was similar to our study results.[10]

Limitations

We did not include a placebo group because pregnancy is a known risk factor for PONV and we cannot afford to

omit any antiemetic to the patients. As we enrolled patients of ASA class I and II in our study, the results may not be generalized to the patients with higher ASA physical status. We did not evaluate PONV after 24 h.

CONCLUSION

Although palonosetron plus dexamethasone is better than granisetron plus dexamethasone in terms of PONV, requirement of rescue antiemetic and patient satisfication score but the cost effectiveness of granisetron makes it a more commonly used drug in a setting with a limited resources. Further studies are recommended to evaluate the effectiveness of this combination therapy in caesarean section under spinal anesthesia to apply the results to the general population.

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