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Case Report

Gastric Submucosal Leiomyoma Managed by Laparoscopic and Endoscopic Cooperative Surgery: A Rare Case Report

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Abstract

Gastric leiomyoma is a rare, benign sub mucosal tumor arising from smooth muscle of stomach. This benign tumor arises from either musclaris propria or muscularis mucosa layers of the stomach wall and seldom from tunica media of vessels forming the vasculature of stomach. It is usually asymptomatic with excellent prognosis. Its discovery is mostly incidental. The pathogenesis of gastric leiomyoma remains indefinite. The treatment of smooth muscle tumors of the stomach is solely surgical resection, since they are radio-resistant. Herein, we describe case of 30-year-old female with no known co morbidities presented with complaints of dysphagia for 4 months which on evaluation led to the discovery of submucosal gastric mass that was subsequently diagnosed as gastric leiomyoma through immunohistochemical markers and managed by laparoscopic excision.

Key words: Benign, Endoscopy, Excision, Laparoscopy, Leiomyoma

INTRODUCTION

The word leiomyoma bearing its origin from Greek translates to smooth muscle tumor. It commonly arises from the body of uterus making extrauterine manifestations, a rarity. Leiomyoma of the gastrointestinal tract is more commonly found in the esophagus where it is the most common benign tumor. Gastric leiomyoma constitutes 0.19% of all neoplasms and about 2.5% of all gastric neoplasm. There is no gender predisposition.[1] These are generally well circumscribed unencapsulated tumors composed of interlacing network of spindle cells of either muscularis propria or muscularis mucosa with low mitotic index which helps in differentiating them from the malignant counterpart, Leiomyosarcoma.

True leiomyomas are strongly and diffusely positive for desmin and smooth muscle actin and negative for CD117 and CD34, the latter two strongly favoring gastrointestinal stromal tumor (GIST) as the diagnosis.[2] This immunohistochemical identity helps in delineation from GIST and schwannomas, the most common subepithelial gastric masses that gastric leiomyomas are commonly confused with. They exhibit benign biological behaviors by rarely metastasizing to lymph node or any adjacent organ. These slow growing tumors seldom produce symptoms and thus are usually encountered incidentally while endoscopic procedures for other purposes.

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CASE REPORT

A 30-year-old female, with no known comorbidities, presented with complaints of dysphagia for 4 months duration. She gave no history of hematemesis, melena, or symptoms suggestive of obstruction (vomiting, constipation, and early satiety) there was no history of loss of appetite or significant weight loss. No abnormal family or menstrual history was given. Medication refractory dyspepsia warranted further evaluation to arrive at a cause. Upper GI scopy showed a large, well circumscribed non ulcerated submucosal mass near the lesser curvature of

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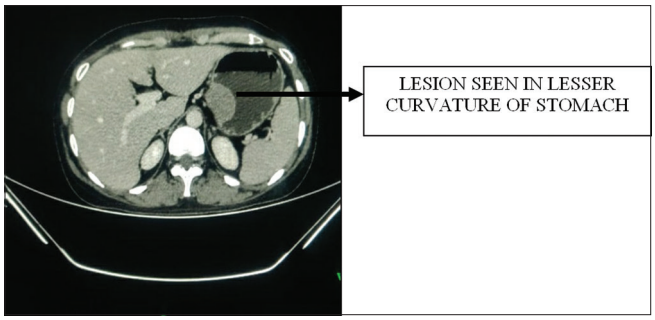

Figure 1: Gastric leiomyoma-axial section

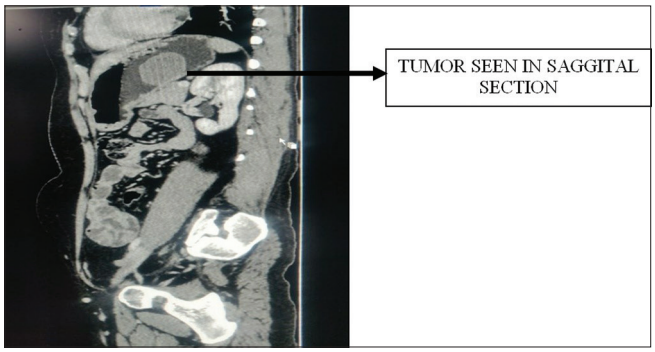

Figure 2: Gastric leiomyoma - saggital section

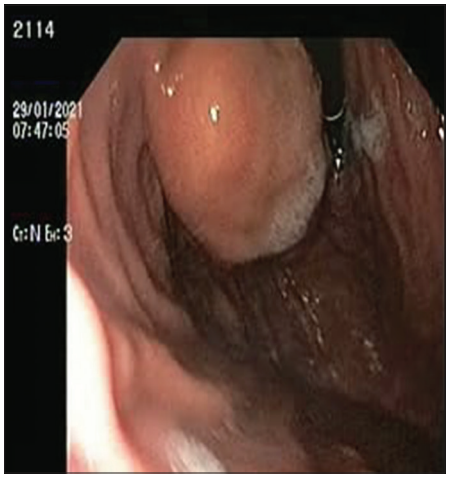

Figure 3: Per-operative upper gastrointestinalscopy showing well circumscribed mass projecting intraluminal in lesser curvature of stomach 2 cm from OG junction-as seen in j manovoure

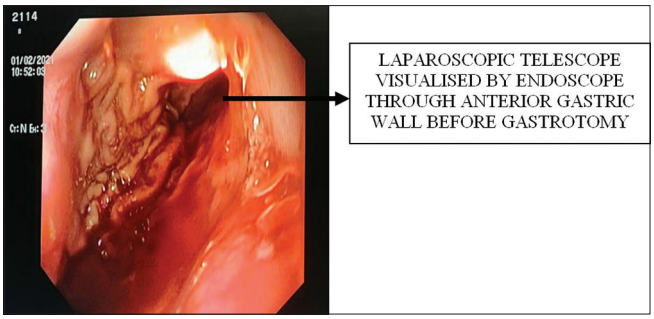

Figure 4: Gastric leiomyoma-pre-operative endoscopic view

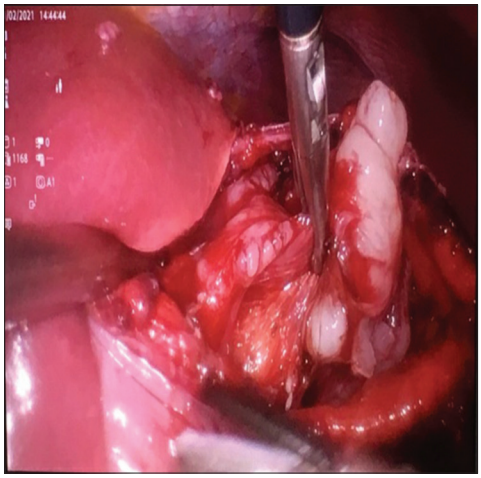

Figure 5: Gastric leiomyoma - laparoscopic pre-operative picture

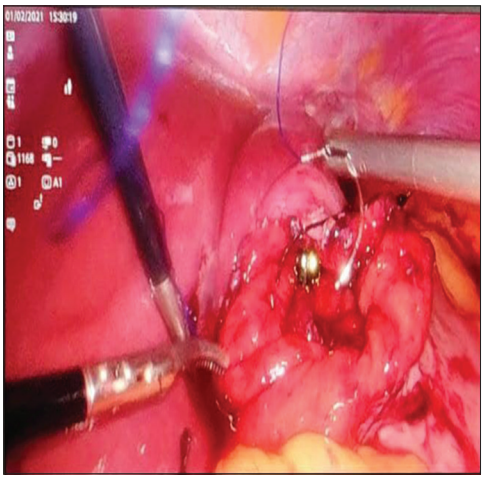

Figure 6: Gastic leiomyoma – pre-operative laparoscopic suturing of tumor resected site

the stomach 2 cm from OG junction associated with antritis and duodenitis. Ultrasound of abdomen and pelvis revealed an incidental finding of anterior myometrial uterine fibroid of size 27 × 18 × 19 mm with focal anterior adenomyosis. The liver was normal in size and echo texture and no ascites was noted. Contract computed tomography (CT) of the abdomen showed (Figures 1 and 2) an intramural, homogenous, circumferential lesion occupying the gastroesophageal junction, right cardia, and lesser curvature. This mass of size 5 cm in length and 2.9 cm in thickness with smooth margins caused focal minimal narrowing with no proximal dilation of esophagus. Routine investigations were carried out on admission. Blood cell work up revealed a normal hemoglobin of 12.4 g/dl. There was no derangement in other blood parameters as well. Liver function test, coagulation profile, renal function test, and electrolytes were within normal limits. According

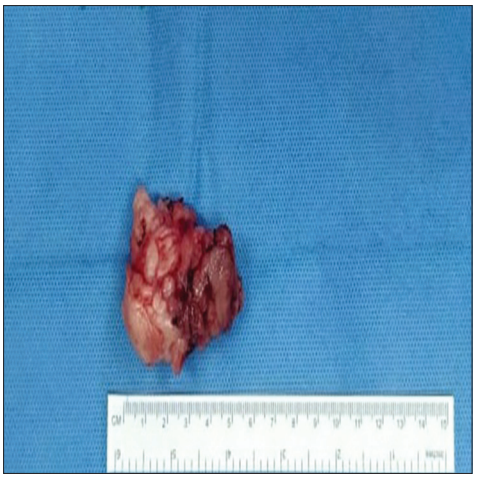

Figure 7: Gastric leiomyoma- specimen

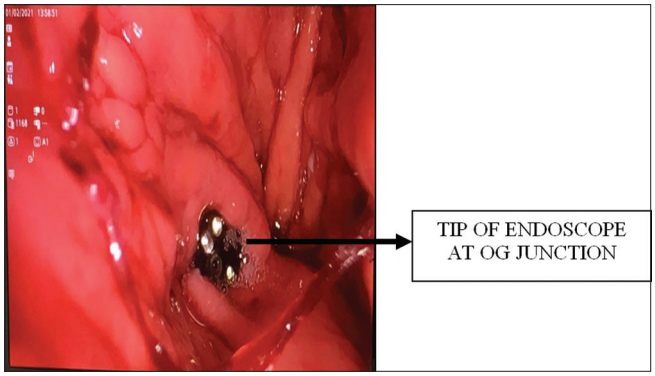

Figure 8: Gastric leiomyoma – pre-operative laparoscopic picture

to American Gastrointestinal Association (AGA) any sub epithelial gastric mass of size more than 3 cm has to be surgically excised even without a definitive pre-operative diagnosis. Ergo with the provisional diagnosis favoring GIST, patient was planned for surgical excision: Procedure name-Laparoscopic and Endoscopic Cooperative Surgery. Under general anesthesia, patient in supine position, 10 mm port was placed in supraumbilical region, three 5 mm ports were placed in epigastric, right hypochondriac and left hypochondriac region, respectively. Per-operative endoscopy (Figures 3 and 4) helped us to precisely identify the upper margin of tumor and confirmed no involvement OG junction and helped us to precisely mark the line of incision with 1cm margin all around and stabilization of tumor with a snare. Anterior gastrotomy was done by a vertical incision with harmonic scalpel. Stay sutures were taken on either side of tumor. Incision was made with harmonic scalpel in the posterior wall of gastric mucosa 1 cm away from tumor on all. Plane was created beneath the tumor. Excision was done (Figure 5). Posterior wall of stomach was intact (muscularis propria seen clearly on the floor). Mucosal edges were closed with 2-0 vicryl suture (Figure 6). OG junction was found to be intact. Anterior gastrotomy was closed with 2-0 PDS with continuous sutures. First and second layer was closed with 2–0 silk with inverted seromuscular sutures. Specimen was retrieved with endobag . (Figure 7). Ports were closed and endoscopy removed. Histopathological examination of the surgical specimen showed spindle cell type gastrointestinal tumor with no necrotic area and low mitotic rate (<5/5 mm^2). On immunohistochemical staining, the specimen was negative for c-kit/CD117 and DOG-1 but positive for smooth muscle actin a sensitive antigen for myoepithelial differentiation. With the cell of origin being confirmed to be smooth muscle, a definitive diagnosis of gastric leiomyoma was made which has excellent prognosis. Post-operative period was uneventful with good recuperation (Figure 8).

DISCUSSION

Extrauterine leiomyoma are rare, even more so in the gastrointestinal tract. In GI tract, they are common in the esophagus. Gastric leiomyoma despite being rarity in terms of its overall occurrence is the most common benign mesenchymal tumor in stomach accounting for 2% of all resected neoplasms of stomach.[2] It is frequently observed in individuals between 50 and 70 years of age. No gender predilection has been noted, although a study conducted by Peter and Jorge found this tumor to be common amongst men.[2] It is often sporadic in its occurrence, although familial incidence is observed as part of syndromes such as Alport and Werner's.[3] This benign tumor arises from either musclaris propria or muscularis mucosa layers of the stomach wall and seldom from tunica media of vessels forming the vasculature of stomach. The pathogenesis of gastric leiomyoma remains indefinite.

Gastric leiomyoma is one among intramural gastric masses. The most common intramural gastric-mass is GIST which originates from interstitial cells of Cajal in the myenteric plexus. Previous literatures used GIST and leiomyoma interchangeably but with the advent of endoscopic ultrasound and immunohistochemistry their delineation has become easier. This is important for GIST is more inclined toward a malignant evolution when compared to leiomyoma. GIST and Schwannoma are common differential diagnosis for this condition. True leiomyoma differs from them in several ways. This tumor occurs in patients much younger compared to those with GIST. It is commonly located in the cardiac region while the other two are found in the body of stomach.[4] Leiomyoma very rarely infiltrates adjacent layers of stomach wall or metastasizes to lymph nodes or adjacent viscera as opposed to GIST. The cell of origin varies for the above three despite their mesenchymal origin. Consequently, the tumor cells will show varied positivity on immunohistochemical staining as they reflect cell specific antigenicity.[5] Thus, radiological,

histopathological, and immunohistochemical studies help in arriving at definitive diagnosis.

Clinical presentation of gastric leiomyoma depends on the location and size. These are slow growing tumors and thus patients are generally asymptomatic and found incidentally during endoscopy, surgery or autopsy. When symptomatic patients present with upper GI hemorrhage, manifesting as hematemesis or melena, aggravated by usage of anticoagulants, nonsteroidal anti-inflammatory drugs and steroids. This occurs when the growing tumor ulcerates the overlying mucosa by means of pressure necrosis. According to a study conducted in Africa, the incidence of spontaneous gastrointestinal bleeding in gastric leiomyoma is relatively high and frank severe hematemesis is more likely to be due to leiomyoma than due to carcinoma of the stomach.[6,7] Patients also complain of atypical epigastric pain and nonspecific dyspepsia. Obstructive symptoms are very rare and occur when the large wide based antral tumor encroaches on the pylorus.[6] Frequent hematemesis leads to drop in the hemoglobin. Weight loss is not as commonly seen as in the case of malignancy given the absence of cachexia. In this study, gastric leiomyoma was compounded with fibroid in the uterus. As suggested in the report by Kathleen, the synchronous presentation of leiomyomas lodged at different sites could perhaps adhere to the possibility of multifocal origin rather than a metastasizing benign focus.[8,9]

Leiomyoma of stomach like other sub epithelial gastric mass is evaluated by endoscopy. Endoscopically, leiomyomas appear as smooth, well-defined tumors, with stretched and effaced mucosal folds overlying the lesions, also referred to as the Schindler's sign. Endoscopy gives an insight into the morphology of the lesion (size, shape, and mobility), while endoscopic ultrasound helps in differentiating intra mural from extramural lesions. Endoscopic ultrasound apart from showing the layer of origin, exposes any infiltration into serosa or adjacent structures. Contrast CT and magnetic resonance imaging also show the origin, extent and possible metastasis of sub epithelial masses but unlike endoscopic ultrasound cannot delineate the layers of gastric wall. To arrive at definitive preoperative diagnosis, these have to be supplemented by histopathological studies.

Tissue diagnosis can be made using endoscopic guided fine-needle aspiration cytology, Endoscopic ultrasound guided core needle biopsy or staked biopsy.[10] These methods have their own shortcomings. Endoscopic biopsies rarely provide a diagnosis because lesions in the submucosa are beyond the reach of the standard forceps. This is circumvented to some extent by performing staked biopsy. A study conducted in the US found Endoscopic submucosal-mucosal resection to be a better alternative over the jumbo forceps in acquiring substantial amount of tissue sample.[11] Immunohistochemical study is the latest advent in the path towards definitive diagnosis. Leiomyomas are diffusely positive for smooth muscle antigen desmin and smooth muscle actin while turning negative for C-kit, Dog1, and S-100. CD117 and Dog1 are specific for GIST while S-100 is for schwannoma. Given this difficulty even without definitive diagnosis open or laparoscopic surgery is considered gold standard.

The treatment of smooth muscle tumors of the stomach is solely surgical resection, since they are radio-resistant.[12] According to the AGA, patients with submucosal tumors <3 cm may be followed up by periodic Esophagogastroduodenoscopy or endoscopic ultrasound examinations, while lesions >3 cm, in which the malignant potential cannot be determined by less invasive, means it requires surgical or endoscopic excision for diagnosis.[13] National comprehensive cancer network guidelines suggests all gastric stromal tumors of size more than 2 cm to be resected while those found incidentally measuring <2 cm to either be resected or subjected to surveillance. The place of conventional open surgery in the removal of these benign tumors has reduced. Patients can now benefit from the Minimally Invasive Surgery, through laparoscopy. This method of treatment has the advantages of less pain, shorter period of recovery, better immune response, and earlier discharge. Endoscopic resection or endoscopic submucosal dissection is the recent advances popularized in Japan in the field of therapeutic endoscopy. They can serve as treatment for older patients with comorbidities, unfit for surgical intervention but they carry the perilous disadvantage of perforation and hemorrhage. Perforation and hemorrhage during endoscopic procedures can be managed well when coupled with laparoscopy. This is done in laparoscopic and endoscopic cooperative surgery which fuses laparoscopy and endoscopy for the resection of gastrointestinal tumor.[14]

CONCLUSION

In our case combined laparoscopic and endoscopic complete surgical resection of tumor has been done with no evidence of recurrence on periodic follow-up.

The patients with surgically resected tumors have a favorable clinical outcome.[1] Where complete surgical excision has been achieved, there has been no reported case of tumor recurrence. Incomplete excision, however, carries the risk of local recurrence of the tumor.[15] Thus, this benign tumor which is surgically amenable has got excellent prognosis.

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Case Report

Pleomorphic Adenoma of Submandibular Salivary Gland: A Case Report of Pleomorphic Adenoma at Rare Location

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Abstract

Pleomorphic adenoma (PA) is the most common salivary gland neoplasm. It mostly occurs in the parotid gland. It occurs rarely in the submandibular or the sublingual gland presenting a case of a large PA at submandibular gland location. Salivary gland neoplasms constitute about 3% of all head and neck malignancies. About 90% of the benign tumors of salivary gland occur in major salivary gland and majority of them occur in parotid gland (80–90%). PA occurring in submandibular and sublingual gland is rare. It contributes to 8–10% of cases. Submandibular gland is second most common site for occurrence of PA and it is also the most common benign tumor that arises from submandibular gland. It occurs more frequently in females than males and most between age 40 and 60 years. Our patient was 56 years old and female. Occurrence of PA in minor salivary gland is rare. Among minor salivary glands palate is the most common site, followed by lips due highest concentration of salivary gland at these sites. Other sites where it may occur are oral cavity, nasal cavity pharynx, and neck. PA is the most tumor arising from salivary gland and majority of them occurs in major salivary gland. About 90% of PA occurs in parotid gland followed by submandibular gland (8–10%). Surgical excision with adequate margin is treatment of choice. Excision of tumor with inadequate margins may lead to recurrence.

Key words: Pleomorphic adenoma, Submandibular gland, Submandibular salivary gland

INTRODUCTION

Salivary gland tumors are rare and make up to 3% of head and neck tumors.[1] Approximately 90% of the benign neoplasm of the major salivary gland is associated with the parotid gland. Pleomorphic adenoma (PA) comprises 80–90% of these benign parotid neoplasms. PA of the submandibular and sublingual gland is quite uncommon and comprises rest (8–10%) of the group.[2] In a recent Asian study, Subhashraj in his single institutional review of 422 benign cases of benign salivary gland tumors has reviewed 422 benign cases.[3] Out of these, 363 tumors were PA (86%). Of these 363 cases of PA, 203 involved the parotid (56%), 72 involved the submandibular (20%) and one involved the sublingual gland (0.2%). The rest had an origin from the minor salivary glands. This case report presents a case of a histologically proven PA involving the submandibular gland. The case was treated surgically and followed up for more than 2 years with no recurrence.

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CASE PRESENTATION AND TREATMENT

A 56-year-old female presented with painless swelling in the right side of neck which slowly increased in size for the past 2 years. Patient also had burns mark present over the swelling [Figure 1]. The swelling measured 12 × 10 cm, firm in consistency, mobile, adherent to overlying skin with no intraoral extension on bimanual palpation. MRI of face and neck showed a well-defined globular swelling arising from the right submandibular gland measuring 13 × 10 cm, with well-defined capsule, compressing the carotid sheath with no definitive infiltration [Figure 2]. No cervical lymph nodes were enlarged. FNAC done from the swelling reported as PA. Patient planned for excision of right submandibular gland PA under GA. Epllitical incisional was made around the scar mark on neck and flaps were raised in subplatysmal, supravenous plane. Right facial artery and

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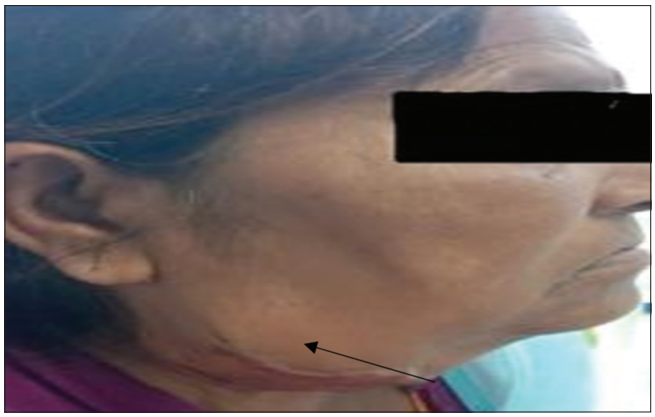

Figure 1: Clinical picture of patient. Patient presented with a large, painless, and mobile swelling in the neck with no intraoral extension. Burn scar mark noted over the swelling

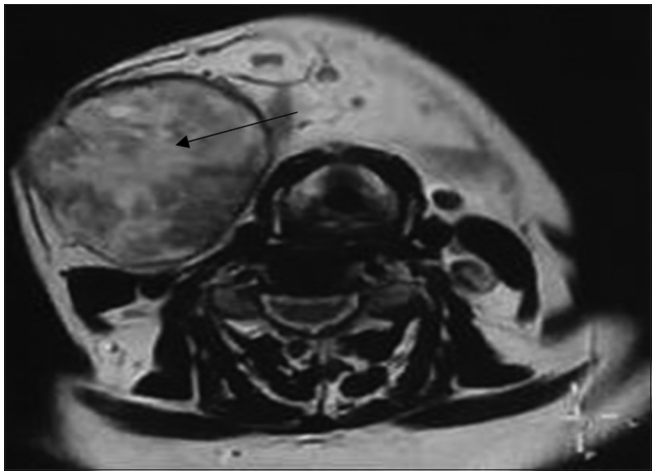

Figure 2: Magnetic resonance imaging of face and neck showed well defined globular swelling in the right side of neck measuring 13 × 10 cm, with well-defined capsule, compressing the carotid sheath with no definitive infiltration

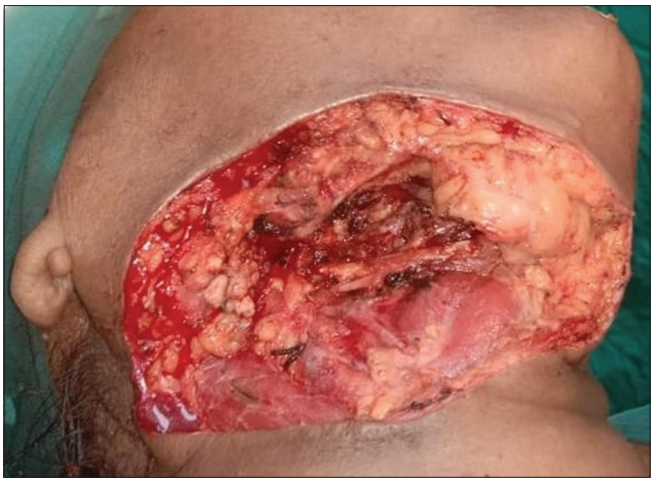

Figure 3: Intraoperative picture of the neck after removal of submandibular gland tumor

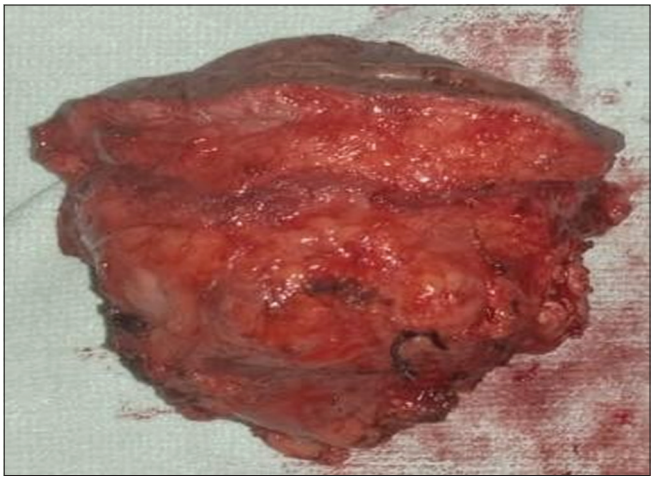

Figure 4: Excised specimen of submandibular salivary gland tumor with scarred skin

vein were identified and ligated and right submandibular gland was excised in to along with overlying scarred skin preserving hypoglossal and ligual nerve [Figures 3 and 4]. Primary closure of platysma and skin was done. Biopsy was reported as PA. Patient had no recurrence after 1 year follow-up [Figure 5].

DISCUSSION

Salivary gland neoplasms which constitute about 3% of all head and neck malignancies.[1] About 90% of the benign tumors of salivary gland occur in major salivary gland and majority of them occur in parotid gland (80–90%). PA occurring in submandibular and sublingual gland is rare. It contributes to 8–10% of cases.[2] Submandibular gland is second most common site for occurrence of PA and it is also the most common benign tumor that arises from submandibular gland.[4] It occurs more frequently in females than males and most between age 40 and 60 years.[5] Our patient was 56 years old and female. Occurrence of PA in minor salivary gland is rare. Among minor salivary glands palate is the most common site, followed by lips due highest concentration of salivary gland at these sites.[6-8] Other sites where it may occur are oral cavity, nasal cavity pharynx, and neck.[9,10]

PA is diagnosed by FNAC/biopsy. It is also named as "mixed tumuor" because of its morphology seen under microscope. The tumor is composed of both epithelial and stromal components. Outer layer consists myoepithelial and epithelial cells and inner layer is mesenchymal in origin. Inner layers consist of stromal cells which may contain hyaline, myxoid, mucoid or cartilage tissue.[11] The tumor is surrounded by a pseudocapsule which consists of fibrous tissue and they are non-enveloped. The tumor has

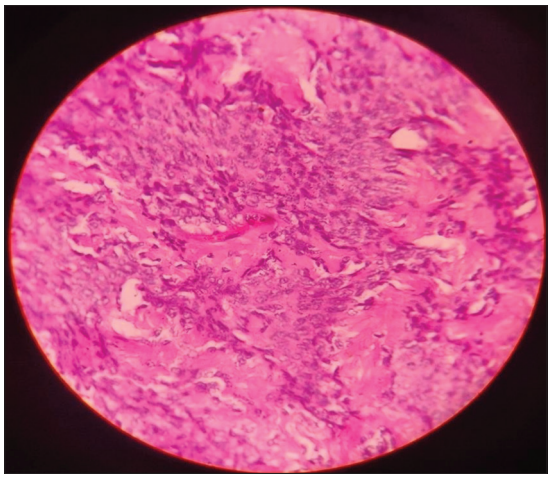

Figure 5: Histopathological examination showing the presence of both epithelial and mesenchymal cells

pseudopods which penetrate through the pseudocapsule. If tumors are not excised with adequate margins, remnant pseudopods may lead to recurrence.[12]

Treatment of choice for PA is surgical excision with adequate margin. In our patient elliptical incision was made to include the scarred skin. For submandibular gland excision, horizontal incision should be made 4 cm below the angle of mandible to avoid injury to marginal mandibular nerve and facial artery should ligated twice. First ligation done after identifying marginal mandibular nerve above the submandibular gland to avoid injury to nerve and second ligation is done below the gland at the origin of facial artery from external carotid artery. PA may turn malignant in 25% of cases and it is known as carcinoma ex PA.[13] Therefore, early diagnosis and surgical treatment are recommended. Adjuvant radiotherapy can be used for patients with incomplete resection, positive margin, and recurrent cases after excision.[14]

CONCLUSION

PA is the most tumor arising from salivary gland and majority of them occurs in major salivary gland. About 90% of PA occurs in parotid gland followed by submandibular gland (8–10%). Surgical excision with adequate margin is treatment of choice. Excision of tumor with inadequate margins may lead to recurrence.

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Case Report

A Rare Case of Retroperitoneal Lipoblastoma with Review of Literature

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Abstract

Lipoblastoma is a rare benign pediatric mesenchymal neoplasm. Common locations include extremities and trunk, while retroperitoneal location is very rare and only <30 cases have been reported worldwide. Retroperitoneal lipoblastomas tend to present as a large, rapidly growing abdominal mass that can be challenging to diagnose preoperatively. Thorough investigations and histopathological examination are imperative to arrive at the correct diagnosis, thus ensuring appropriate treatment to the patient. Here, we report a case of 2-year-old boy who presented with a large abdominal mass compressing the adjacent structures. On resection and histopathological evaluation, a diagnosis of lipoblastoma was made.

Key words: Abdominal mass, Lipoblastoma, Pediatric, Retroperitoneal

INTRODUCTION

Lipoblastoma is a rare benign pediatric neoplasm of embryonal fat seen mostly in infants and children below 3 years of age.[1] The most common sites include trunk and extremities, whereas retroperitoneal lipoblastomas are relatively rare, accounting for <5% of all cases.[2-4] The clinical presentation of retroperitoneal lipoblastomas is similar to malignant tumors, most commonly liposarcoma and teratoma, therefore posing a diagnostic difficulty both clinically as well as radiologically. Lipoblastoma is benign and carries an excellent prognosis on complete excision. Thus, histopathology plays a major role avoiding overdiagnosis and aggressive treatment.

CASE REPORT

A 2-year-old boy presented with gradually progressive abdominal mass for 1 year, associated with abdominal pain, constipation, and vomiting for 1 month along with dribbling of urine and difficulty in micturition for 3 weeks.

The child was initially evaluated in another institute, where imaging studies, biopsy of the mass, and an attempt at surgical resection were made. Ultrasound abdomen showed a large ill-defined irregular echogenic solid mass measuring about 11.7 × 10 cm in the right lumbar region, extending up to right iliac fossa suggestive of neuroblastoma. Computed tomography (CT) abdomen revealed a large almost rounded soft-tissue mass of mixed attenuation in the right lumbar and right iliac region, causing compression of the right hip and displacing bowel loops, suggestive of large germ cell tumor – possibly teratoma. Ultrasound-guided fine-needle aspiration cytology showed fragments of spindle cells, fatty tissue, and fibroid tissue fragments suggestive of spindle cell tumor or nerve sheath tumor. Biopsy of the mass showed atypical epithelial cells with inconclusive diagnosis. Attempt for surgery at the earlier institute resulted only in incisional biopsy as the mass was considered inoperable. HPE showed fibrofatty tissue admixed with few mononuclear cells. No evidence of granuloma or malignancy was noted.

On examination of the child in our hospital, the abdomen was distended by a large palpable mass measuring around

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13 × 12 cm, extending from the right iliac fossa to the right hypochondrium, crossing midline and hard in consistency. Dilated veins and scars were noted in the abdominal wall. Serum alpha-fetoprotein, beta-human chorionic gonadotropin, and urine vanillylmandelic acid were normal.

Positron emission tomography-CT revealed an encapsulated heterogenous mass lesion measuring 18.9 × 13.5 × 15.5 cm in the right anterior pararenal space, with predominantly fat components with interspersed soft-tissue densities. The lesion was seen to cause mass effect on the liver and displacing the right kidney and ureter causing moderate hydroureteronephrosis as well as displacing the bowel loops to the left side, suggesting a diagnosis of liposarcoma [Figure 1].

Exploratory laparotomy was done and intraoperatively, the tumor was found to be adherent to the psoas muscle. The tumor was excised and sent for histopathological examination. The specimen weighed 2.2 kgs and measuring 20 × 19 × 9 cm. External surface appeared gray-yellow and smooth. On cut surface, it appeared pale, gray-white to gray-yellow, and firm in consistency [Figure 2]. On histopathology, multiple sections from the mass showed a fairly circumscribed, partially encapsulated lipomatous lesion showing adipocytes arranged in lobular pattern separated by fibrous stroma composed of oval to spindled cells. Few multivacuolated lipoblasts were noted and focal myxoid areas seen. No evidence of curvilinear blood vessels/atypia/mitoses/necrosis or hemorrhage was seen. A diagnosis of lipoblastoma was made considering the age of the patient [Figure 3a and b].

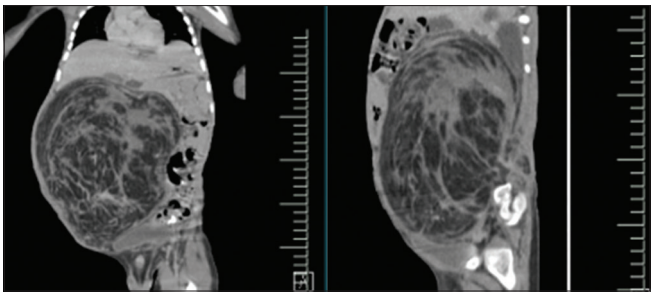

Figure 1: Positron emission tomography-computed tomography images showing a large heterogenous mass lesion in the right anterior pararenal space

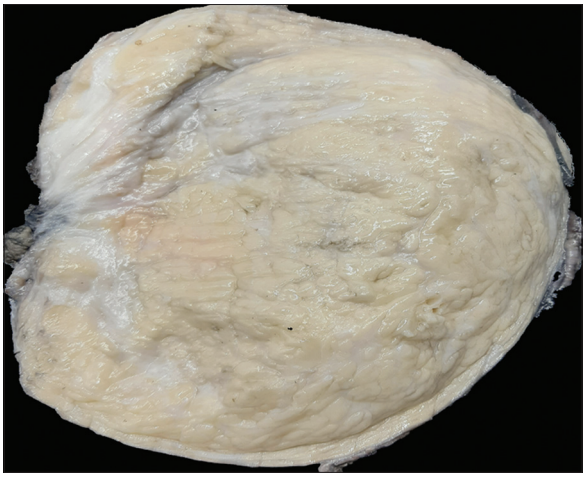

Figure 2: Cut surface of lesion appearing pale, gray-white to gray-yellow and firm

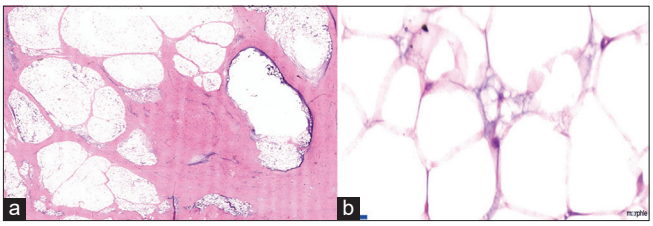

Figure 3: (a) Hematoxylin and eosin (H and E), 40×: Lobular pattern of arrangement of adipocytes, separated by fibrous stroma composed of spindled out cells. (b) H and E, 400×: Lipoblast with multivacuoalted cytoplasm and central round nucleus

DISCUSSION

Lipoblastoma is a rare benign neoplasm of embryonal white fat, which can present as a localized well-circumscribed tumor or as a diffusely infiltrative, multicentric form called lipoblastomatosis, seen predominantly in deeper tissues.[2,5,6] It occurs mostly in infancy and early childhood, with 75–90% of cases occurring before 3 years. Sporadic examples have also been reported in older children and adolescents and very rarely in adults. Most studies have reported a slight predilection for this tumor in males.[2] Most commonly involved sites include the subcutaneous tissues of trunk and extremities. Lipoblastoma may arise in a variety of locations including abdomen, mesentery, retroperitoneum, pelvis, inguinoscrotal or labial region, perineum, mediastinum, and head and neck region.[2,7-9] However, retroperitoneal location is very rare, accounting for <5% of all cases with less than 30 well-documented cases reported worldwide.[3,9] Recent studies by Gerhard-Hartmann *et al.* as well as Sakamoto *et al.* documented a total of 23 and 26 cases, respectively, reported worldwide.[9,10]

Lipoblastomas are typically 2–5 cm in diameter; however, retroperitoneal lipoblastomas are reported to be rapidly growing and commonly attaining an enormous size. Studies by Burchhardt *et al.* and Kok *et al.* have documented cases of retroperitoneal lipoblastomas measuring up to 25 cm in greatest dimension.[2,3,11] Lipoblastomas commonly present as painless superficial soft-tissue masses; however, some large abdominal or mediastinal tumors can impinge on and compress adjacent organs, nerves, or blood vessels, causing pain as well as compromised function and also have a propensity for local invasion.[12] Hence, such a presentation, especially in retroperitoneal location,

can often mimic malignant tumors clinically as well as radiologically. Pre-operative diagnosis of retroperitoneal lipoblastoma can be very challenging and the major differential diagnoses include sarcomas, Wilm's tumor, neuroblastoma, and teratoma. Investigative work-up can include assay of tumor biomarkers, ultrasonography to detect tumors with high fluid content and vascularity, CT scans for mass characterization and lymphadenopathy detection, and magnetic resonance imaging (MRI) for anatomic delineation.[2,3] Although radiological imaging can be helpful in narrowing down the diagnosis to lipomatous tumors, accurate differentiation of immature, and mature adipocytes on any imaging modality is difficult.[5] However, MRI has been reported to be the best radiological method due to its increased sensitivity for lipoblastoma which shows increased vascularity that presents as a lower intensity on T1-weighted images in comparison with lipoma.[13] Due to the various limitations of imaging modalities, an accurate pre-operative diagnosis is rarely made and surgical resection followed by histopathological examination remains the key for the definitive diagnosis of lipoblastoma.[5,10]

On gross examination, lipoblastomas are typically soft, lobulated, yellow-white to tan masses appearing paler than the ordinary lipoma, and may have myxoid nodules, cystic space or fat nodules separated by fibrous septa.[2,11] Histopathologic examination characteristically demonstrates lobular architecture with sheets of adipocytes separated by fibrovascular septa. The adipocytes show a spectrum of maturation, ranging from primitive, stellate to spindled mesenchymal cells to multivacuolated, or small signet ring lipoblasts to mature adipocytes.[2] Prominent myxoid change with a plexiform vascular pattern can also be seen reminiscent of myxoid liposarcoma, making it a close differential diagnosis. However, myxoid liposarcoma shows minimal lobulation with centrifugal loss of maturation and increased cellularity with focal pleomorphic nuclei, whereas lipoblastomas lack nuclear atypia altogether. Other major histological differential diagnosis includes well-differentiated liposarcoma/atypical lipomatous tumor which has prominent spindle cells with large, deep-staining nuclei, and marked nuclear enlargement or pleomorphism. However, both myxoid liposarcoma and well-differentiated liposarcoma are commonly seen in adults and very rare in pediatric age group with cases typically occurring in children older than 5 years. Benign tumors such as lipoma, fibrolipoma, hibernoma, lipofibromatosis, and fibrous hamartoma of infancy share common histological features with lipoblastoma, but they lack lipoblasts.[14]

Recent use of cytogenetic analysis for detection of PLAG1 gene rearrangement is useful for the accurate diagnosis of lipoblastoma in cases with suspicion of myxoid liposarcoma. [7] Three fusion partner genes known in relation to PLAG1 in lipoblastoma are: HAS2 at 8q24.1, COL1A2 at 7q22, and RAD51L1 at 14q24. In addition, two novel fusion genes COL3A1- PLAG1 and RAB2A-PLAG1 have been identified by Yoshida *et al*.[15] In contrast, myxoid liposarcomas show characteristic t(12;16) translocation. Cytogenetic analysis was not done in our case as there was no diagnostic suspicion.

Lipoblastoma has an excellent prognosis after complete surgical excision, despite rapidly enlarging size and tendency for local invasion.[7] In cases where resectability is questionable due to involvement of critical structures, a staged surgical approach has been recommended by Speer *et al*.[3,12] No cases of metastases have been reported and the rate of recurrence is 13–46%, with recurrence predominantly attributable to incomplete excision.[2]

CONCLUSION

Retroperitoneal lipoblastoma is a rare benign infantile and pediatric neoplasm. It can be diagnostically challenging, both clinically and radiologically; thus, histopathological features play a key role at clinching the diagnosis. As it presents as a rapidly enlarging abdominal mass mimicking other soft-tissue tumors, accurate diagnosis and timely management are essential.

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Case Report

Surgical Management of Mandibular Anteriors with Apicectomy and Guided Bone Regeneration: A Case Report

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Abstract

Periodontal surgery is a safe and adequate alternative when teeth are not responding to conventional endodontic treatment. Sometimes endodontic failure causes lesions such as periapical cyst. Periodontal surgery comprehends a set of procedures recommended in periapical diseases treatment, when traditional endodontic therapy does not obtain favorable outcomes. In this case report, the treatment of periapical cyst caused by endodontic failure is presented using apicectomy and guided bone regeneration technique. A 54-year-old woman visited the Department of Periodontology with complaint of pain in lower anteriors since 4–5 months. On examination and investigation, periapical cyst was diagnosed. Re-endodontic treatment was done followed by apicectomy in the lower anteriors. Guided bone regeneration procedure was carried out using NovaBone graft and collagen membrane. Apicectomy followed by guided bone regeneration proved to be a great success of treatment. Six months follow-up, Intra oral peri-apical radiograph (IOPA) showed significant bone fill in the lesion.

Key words: Apicectomy, Collagen membrane, Guided bone regeneration, NovaBone putty, Periapical cyst

INTRODUCTION

The aim of endodontic treatment is to eliminate bacteria from root canal system and establish effective barriers against root recontamination.[1] Successful endodontic treatment is achieved only by proper cleaning, shaping, and filling of the entire root canal system and is considered as essential steps. Failure factors in root canal conventional treatment are frequently related to presence of residual bacteria (persistent infection) or reinfection in a previously disinfected canal (secondary infection).[2] Endodontic treatment failures can be related to: extraradicular infections such as periapical actinomycosis;[3] to foreign body reactions that can be caused by endodontic material extrusion;[4] to endogenous cholesterol crystal accumulation in apical tissues;[5] and unresolved cystic lesion.[6] Thus, success relies on different factors and is verified through clinical and radiographic evaluations during follow-up.[2-4,6,7]

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Routine endodontics involve orthograde procedures, but if there is any repeated and resilient infection, the retrograde filling or endodontic surgery is preferred.[8] The periapical tissues repair by either the repair or the regeneration.[9] The repair is by the new tissue and the regeneration is by the original cells. The regeneration is the best method as it will restore the function of the periapical tissue to the previous tissue.[10,11] However, the regeneration is difficult to attain. Various procedures have been considered and implemented to attain the regeneration of the apical tissues in the periapical pathologies of the teeth. In the regenerative methods, the materials such as grafts (bone), autologous platelet concentrates, and barriers that act to prevent the growth of the new tissue, are commonly used.[11] The regenerative procedures are implemented in periodontics, endodontic, and implant surgeries. There are materials that are recently reported with better regeneration than the repair in endodontic surgeries. They are bioabsorbable collagen,

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ePTFEnonresorbable expanded polytetrafluoroethylene, etc. These work by preventing the migration of the cells apically and promoting the regeneration.[10-12]

However, there are various studies that report varying degree of the success using the regenerative methods.[2,3,8-12] Although there are many studies, there have been contrary reports of the success of the regenerative procedure. Thus, this study aims to report a clinical case of an apicoectomy procedure followed by guided bone generation using NovaBone putty and PerioCol as bone graft and membrane, respectively.

CASE REPORT

A 54-year-old woman patient was referred to the Department of Periodontology with pain and labial swelling in the lower anterior region for 2 weeks. The pain was continuous and throbbing. Her medical history was noncontributory. Her dental history revealed endodontic treatment in lower anterior teeth due to pain 4–5 months ago. On examination, soft-tissue revealed labial swelling over 31, 32, 41, and 42 teeth; a sinus opening was seen on the labial aspect of mandibular left central incisor. The area was tender on palpation and the teeth were tender on percussion [Figure 1]. Radiographic examination revealed a large dumbbell shaped periapical radiolucency associated with 31, 32, 41, and 42 [Figure 2]. The periapical lesion resembles a dumbbell shape and was approximately 1.5 cm × 1 cm in its greatest dimensions. Based on the clinical and radiographic findings, mandibular central incisors (31, 32, 41, and 42) were diagnosed as having chronic apical periodontitis with cystic changes. A combined approach of orthograde endodontic treatment for 31, 32, 41, and 42 followed by periapical surgery was planned. The patient was informed about the procedure and consent was taken.

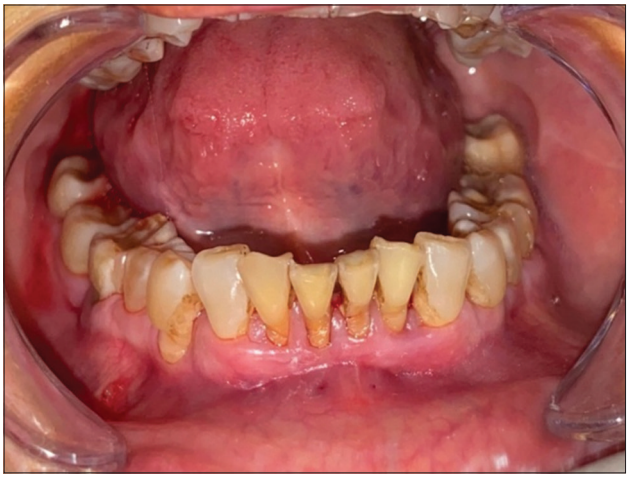

Figure 1: pre-operative clinical picture

Re-endodontic treatment was carried out with 31, 32, 41, and 42. The patient was prescribed antibiotics and analgesics to manage pain and swelling. The patient was prescribed 500 mg of amoxicillin thrice a day for 5 days and combination of 100 mg of aceclofenac and 15 mg of serratiopeptidase twice a day for 5 days. One week later, the patient was asymptomatic, obturation was done with cold lateral compaction technique, and the access cavity was restored with composite resin. Before performing the periodontic surgery, the patient was advised to undergo blood investigations to rule out bleeding disorders. Complete blood picture and coagulation studies report were normal.

Surgical management

After examination, local anesthesia was administered and a full thickness mucoperiosteal flap was elevated under local. A large soft lesion was seen involving the root apices of 41, 31, and 32. The lesion was circumferentially separated from the bony crypt and the teeth [Figure 3]. The granulation tissue in the apical and lateral root surfaces of the mandibular central incisors was removed and root

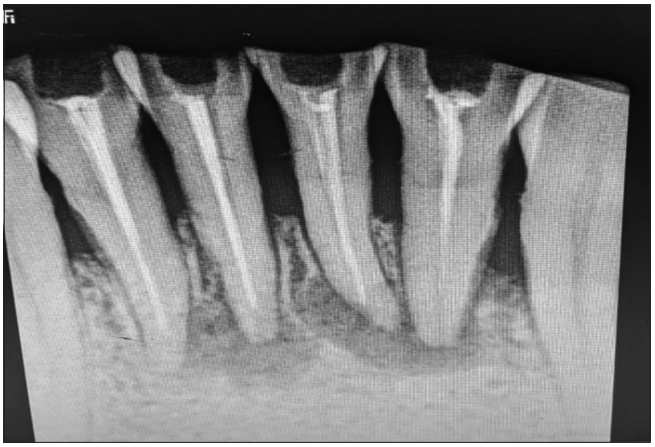

Figure 2: pre-operative radiolucency seen wrt 31, 41, and 42

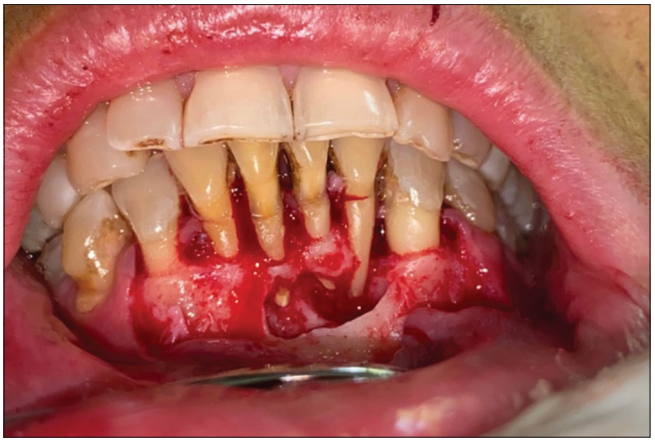

Figure 3: Full thickness flap raised and dumbbell shaped lesion involving 31, 32, 41, and 42 seen

planning done using Gracey curettes. As the extension of the defect was large, NovaBone putty (bone graft) with PerioCol (membrane) was placed. Apical 3 mm of the roots was resected for 31, 32, and 41 and defect was filled with NovaBone putty graft [Figure 4]. The mucoperiosteal flap was sutured in place [Figure 4] and the periapical radiograph was taken for the confirmation of accuracy of grafting of 31, 32, and 41. The patient was periodically reviewed after 1 month, 3 months, and 6 months. The patient was asymptomatic during 6 months follow-up. At 6 months, a radiograph was taken in relation to mandibular central incisors, which confirmed the satisfactory healing of periapical lesion [Figure 5].

DISCUSSION

Periapical cyst can be formed due to persistent chronic infection. Periapical cysts are commonly seen in the mandible and appear as unilocular or multilocular radiolucencies on radiographs. Mandibular cystic lesions can result in bone remodeling weakening the bone and leading to functional changes and predisposing the patient to infection and pathologic fracture.[13]

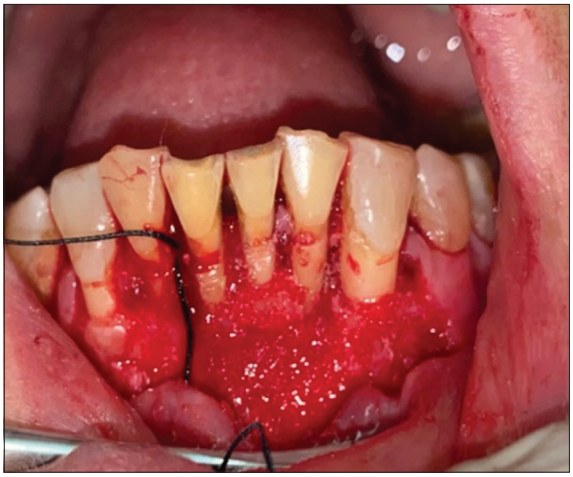

Figure 4: NovaBone putty graft and PerioCol membrane placed with sutures

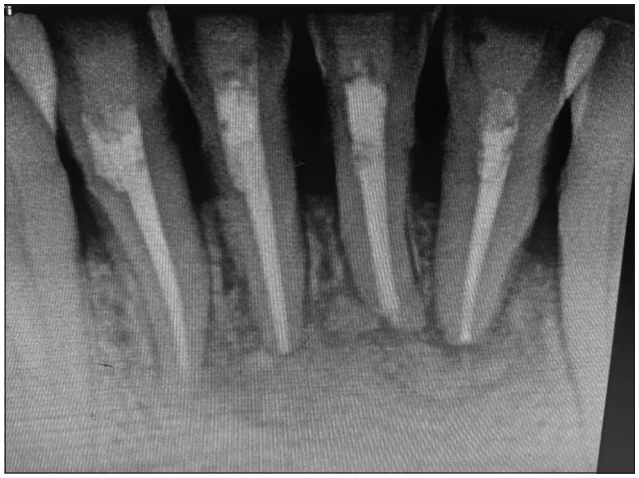

Figure 5: Six months follow-up healing

Periradicular surgery is indicated in obstructed canals, failed endodontically treated cases, extruded root filling materials, and lesions after traumatic injuries. To achieve successful outcome, apicoectomy, periradicular curettage, and root resection are performed during periapical surgery. Long-term Ca (OH)2 therapy is one of the options for treating large cystic periapical lesions as a non-surgical endodontic treatment option. Periapical surgery is considered if non-surgical endodontic therapy fails.

Removal of apical portion of tooth is known as apicectomy. It can be indicated in cases of periapical lesions which stay persistent even after conventional treatment, perforations, fractured instruments, and external absorption presence.[14-16] In this clinical case, the chosen treatment was apicoectomy with curettage and planning, because it was found that the filling was well compacted and then it was chosen not to apply retrograde filling. Leonardi *et al.*[17] stated that several factors can influence apicoectomy success, such as the root region where the apicoectomy is done, the drill type employed or laser execution, as well as the cut angle. It is important to obtain the cut surface as regular as it can. The apical cut must involve anatomical variations such as the presence of isthmuses and accessory canals, because they act as a reservoir for bacteria and necrotic pulp tissue, which can lead to treatment failure. After apicoectomy, it must be observed whether the filling material is not displaced, using a microscope, because failures may be invisible with unaided eyes.

Calcium phosphosilicate (CPS) (NOVABONE) dental putty is a newer next-generation bone graft material built from bioactive glass with additives such as polyethylene glycol (PEG) and glycerin to improve handling and efficacy. On administration, the binder gets absorbed and permits tissue infiltration between the bioglass particles. During healing process, the particles are slowly absorbed and replaced by new bone tissue. This osteostimulation results in new bone formation throughout the grafted site at faster rate than other synthetic materials.

NovaBone is composed of CPS (active ingredient), with PEG as an additive and glycerin as the binder. It consists of two-particle phases: Phase 1 contains bioactive glass particles of 90–710 μ size and Phase 2 contains calcium phosphosilicate of 32–125 μ size. The volume of the active ingredient is approximately 70%. The components are premixed in putty state and delivered as ready-to-use. Both PEG and glycerin are water soluble and are engineered to

be absorbed from the site in 3–5 days. The putty turns tan in color after sterilization.

The putty format allows easier manipulation due to its ready-to-use format. NovaBone is available in various delivery systems as shells, cartridges, and syringes of various sizes with benefits of consistent and reliable bone regeneration. NovaBone putty demonstrates superior performance characteristics that are a result of multiple physical and chemical interactions: "Osteostimulation." Putty has been approved by Food and Drug Administration and CE dental indications in 2007. NovaBone putty is the first synthetic material that required no handling or manipulation and the first to be available in a significantly simplified cartridge delivery system. CPS putty minimizes graft wastage and reduces chair-side time. CPS putty belongs to the class of bioactive regenerative materials that act as an osteoconductive scaffold as well as interacts with the surrounding tissues and imparts an osteostimulatory effect. Moreover, CPS putty is not osteoinductive but a number of *in vivo* studies have demonstrated an accelerated bone formation with CPS particles. Furthermore, the viability and proliferation potential of osteoblasts have been shown to be exemplified in the presence of CPS particles. These CPS particles contain an increased osteocalcin and alkaline phosphatase levels providing a favorable site for bone formation. Osteostimulation is an active process, and CPS dental putty acts as a bone matrix and encourages differentiation of new bone cells at the site. Hence, bone regeneration is hastened by the action of osteostimulation and osteoconduction with simultaneously increasing the resorption rate of the graft material.[18-22]

PerioCol is a collagen membrane which is widely used in regenerative procedures. It contains abundant of collagen fibers and fibroblasts which aids in healing and regeneration.

CONCLUSION

Application of the regenerative procedures in the apicectomy by NovaBone putty and PerioCol collagen membrane helps in better healing after the endodontic surgery as shown in our study. Hence, combination of the materials is recommended for better outcome rather than application of individual material. Six months follow-up showed adequate amount of bone fill.

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Case Report

Subcutaneous Zygomycosis: A Case Report

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Abstract

Subcutaneous Zygomycosis is a rare opportunistic fungal infection caused by Basidiobolus ranarum. The disease occurs due to inoculation of fungal spores into dermis or subcutaneous tissue probably due to minor trauma. It presents usually in healthy individuals, especially in children or adolescent age group as a firm, painless, nodule or sinus on the trunk or the extremities and if untreated can spread locally and enlarge in size. Definitive diagnosis of subcutaneous zygomycosis is made by physical examination together with pathologic and microbiologic evaluation. Extensive surgical debridement along with pharmacological agents like potassium iodide, trimethoprim sulfamethoxazole, amphotericin B, oral azoles or potassium iodide combined with oral azoles have been used to treat subcutaneous zygomycosis. Though this entity is endemic in South India, only limited numbers of cases have been reported. Here we report a case of subcutaneous zygomycosis in a 2 year old boy presenting as recurrent left gluteal swelling.

Key words: Basidiobolomycosis, *Basidiobolus ranarum*, Zygomycosis

INTRODUCTION

Zygomycosis is an acute or chronic infection caused by several fungal agents belonging to the class Zygomycetes which includes two fungal orders: *Mucorales* and *Entomophthorales*, with extremely different pathogenic potentials. *Mucorales* affect only the immunocompromised causing mortality in excess of 60% in those affected, while *Entomophthorales* affects the immune competent and includes *Basidiobolus ranarum* causing subcutaneous zygomycosis and Conidiobolus coronatus causing rhinofacial zygomycosis.[1,2] Entomophthoromycosis is characterized by the formation of firm and non-tender swelling, generally on the extremities, trunk, and rarely over other parts of the body.[3] Although, the organism is found world-wide, only around 100 cases have been documented.[4] Here, we report a child with subcutaneous zygomycosis presenting with swelling in the left gluteal region recurring after excision biopsy.

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CASE REPORT

A 2-year-old boy from rural Tamil Nadu, presented with recurrent swelling over left gluteal region. It started as a small papule which gradually progressed in size over 3–4 months. The swelling was painless, non-itchy, not associated with discharge or changes over overlying skin except for mild hyperpigmentation. Routine blood investigations, blood sugar, and ultrasound examination were normal. He received repeated courses of topical and systemic antibiotics and anti-inflammatory agents but showed no improvement. Magnetic resonance imaging done showed ill-defined T1 hypointense/heterogeneously T2 hyperintense subcutaneous lesion 4.7 × 4.8 × 2.6 cm with diffusion restriction and areas of necrosis with no bony involvement. With a suspicion of soft-tissue tumor, excision biopsy of the entire swelling was done which was reported as panniculitis.

Child presented to us with prompt recurrence of the swelling within a month of complete excision at same site 1–2 cm above the previous lesion scar [Figure 1]. It was progressive, 4 × 5 cm in size at presentation, non-tender, indurated with smooth, and rounded edges over left gluteal area. Skin over the swelling was hyperpigmented and skin could not be pinched away from the swelling and had no evidence of punctum/discharge/sinus or regional lymphadenopathy. Scar of

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the previous excision was healed and unaffected. There were no constitutional symptoms, limitation of hip movement, recent weight loss, similar family history, animal bites or thorn pricks or trauma or vaccination in the site or any other significant medical history. Blood investigation revealed microcytic hypochromic anemia, normal erythrocyte sedimentation rate and serum immunoglobulin E. Review of the histopathological slide

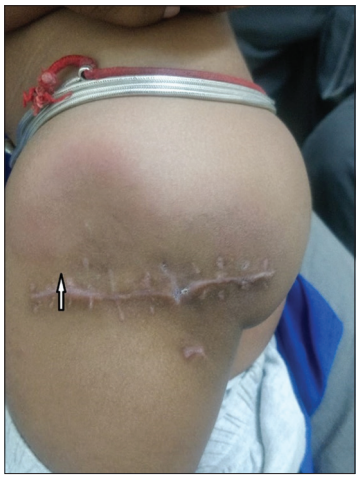
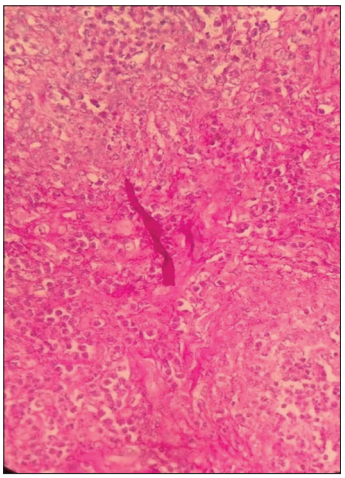


Figure 1



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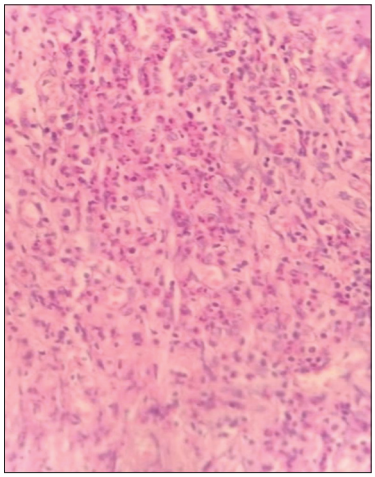

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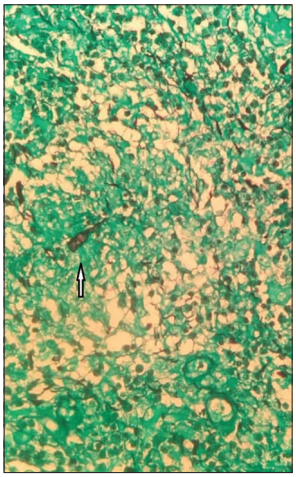

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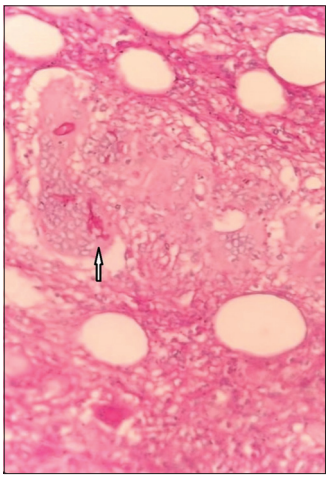

Figure 3

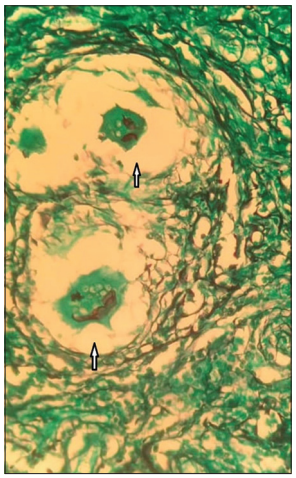

Figure 6

revealed plenty of eosinophils along with foreign body giant cells in hematoxylin and eosin staining [Figure 2]. There were foci of aggregates of epitheloid histiocytes and multinucleate giant cells forming granuloma which were occasionally suppurative. Few giant cells showed broad aseptate hyphae, highlighted by Periodic acid-Schiff stain [Figures 3 and 4] and Grocott-Gomori methanamine silver stain [Figures 5 and 6], and hence, a diagnosis of zygomycosis was made. Following the diagnosis, the child was started on potassium iodide. The child responded well to treatment given and showed good resolution by 6 weeks.

DISCUSSION

B. ranarum was initially described from animal and environmental sources as early as 1886. The first human case of subcutaneous zygomycosis was reported in 1956 in a patient from Indonesia.[4] Subcutaneous zygomycosis is a sporadic fungal infection that is largely restricted to tropical areas of Africa, Asia, and South America.[3] The disease is endemic in southern states of India. The disease usually occurs in children, less often in adolescent age group, and rarely in adults. Males are more frequently affected than females.[5]

The fungus *B. ranarum* is present in soil, decaying vegetable matter, and the intestines of amphibians, reptiles, fish, and insectivorous bats.[6] Subcutaneous zygomycosis results from inoculation of fungal spore into the dermis or subcutaneous tissue. Possible mode of transmission is minor trauma which may be through insect bite, intravenous catheter, or even intramuscular injection.[2]

Basidiobolomycosis occurs commonly in healthy individuals. *B. ranarum* causes a chronic infection of subcutaneous tissue, usually on the arms, trunk, and buttocks with most common presentation being on the thighs and buttocks in a "bathing suit" distribution.[4] It manifests clinically as a firm, painless, disciform nodule on the trunk or the extremities, which if untreated may enlarge in size and spread locally, but systemic dissemination is uncommon.[7]

The definitive diagnosis of basidiobolomycosis requires an excellent physical examination together with both pathologic and microbiologic evaluation.[6] Histologically, subcutaneous Zygomycosis is characterized by small foci of suppurative granuloma distributed all over the dermis and subcutis. Different types of cells including lymphocytes, histiocytes, plasma cell, and multinucleated giant cells contribute to the composition, but eosinophils play the major role, attributed to the release of IL4 and IL10 that help in recruiting eosinophils to the target site. The presence of eosinophilic infiltrate within the granuloma is so characteristic that it is also called as eosinophilic granuloma. Degranulation of these eosinophils leads to the formation of eosinophilic sheath (Splendore-Hoppelli phenomenon) surrounding aseptate or infrequently septate thin walled hyphae. Growth in standard fungal culture medium such as sabouraud dextrose agar is gold standard for confirming the disease if histopathology reveals doubtful results.[2] In addition to culture, diagnosis can be done by detecting an immune response in an immunodiffusion test developed for the diagnosis of basidiobolomycosis. This test has also been useful for monitoring the patients. Serology has been useful in making a diagnosis of disease even in the absence of culture.[8]

Extensive surgical debridement along with systemic antifungals is the standard treatment for cutaneous zygomycosis. Surgical debridement consists of complete resection of necrotic and infected tissue, often with a cuff of uninfected tissue. The wound must be closely monitored and at the first indication of disease progression, surgery must be repeated.[9] Pharmacological agents that have been used to successfully treat this infection include, most commonly potassium iodide, trimethoprim-sulfamethoxazole, amphotericin B, oral azoles, or potassium iodide combined with oral azoles. Treatment of Basidiobolus is not always successful, and no single drug has proved effective in the treatment of all cases.[6,10,11]

Basidiobolomycosis is a great mimicker of soft-tissue tumor, synovial sarcoma, and Burkitt's lymphoma. Hence, the possibility of misdiagnosing this disease as a neoplasm should be kept in mind.[2] It may also resemble tropical infections, fungal (Pythiosis and Sporotrichosis), parasitic (Filariasis and Onchocerciasis), and even bacterial infections (*Mycobacterium tuberculosis* and *Mycobacterium ulcerans*). Subcutaneous zygomycosis is a rare cause of soft-tissue infection and should be suspected in any atypical swelling, chronic non-healing sinuses and abscesses which are refractory to treatment.[12]

CONCLUSION

Subcutaneous zygomycosis is a rare opportunistic fungal infection caused my basidiobolus ranarum. Early diagnosis and awareness of this disease even in non endemic part of the country is very important to prevent misdiagnosis, disfigurement of the tissue, avoidance of unnecessary investigations and surgical interventions.

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Original Article

Effect of Duration of Exercise on VO2 Max and Endurance

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Abstract

Introduction: Regular long-term exercise increases VO2 max by increasing stroke volume and arteriovenous oxygen difference. Exercise increases quantity and activity of key enzymes of glycolysis and thus endurance.

Objectives: The objective of this study was to assess the cardiorespiratory fitness using VO2 max and endurance (fatigue index) in healthy males who are involved in regular exercise in gymnasium for ≤1 year (Study group A), for 1–5 years (Study group B) and in sedentary healthy males (Study group C), to compare the VO2 max and endurance among, Study group A, Study group B, and Study group C, and to correlate effect of duration of exercise on VO2 max and endurance.

Materials and Methods: Estimation of VO2 max is done by Bruce Treadmill Test and endurance is done by Harvard step test in 90 healthy males in the age group of 18–35 years after approval from the Institutional Ethics Committee.

Results: The VO2 max is 18.3 times higher in Group A compare to Group C and 196 times higher in Group B compared to Group C ($P < 0.0001$). The endurance is 2.75 times higher in Group A compared to Group C ($P < 0.07$) and 11 times higher in Group B compared to Group C ($P < 0.0001$).

Conclusion: In the present study, we found that there is statistically significant improvement in VO2 max and endurance with duration of exercise. Hence, regular exercise improves the VO2 max and endurance.

Key words: Cardiorespiratory fitness, Endurance, Exercise, Fatigue index, VO2 max

INTRODUCTION

A nonlinear decline in cardiorespiratory fitness occurs with advancing age when not accompanied by regular exercise.[1,2] Cardiorespiratory endurance is related to the ability of body to sustain prolonged and rhythmic exercise.[3] Regular long-term exercise increases cardiorespiratory fitness.[2]

Cardiorespiratory fitness is globally evaluated as maximum oxygen uptake (VO2 max) that reflects the amount of oxygen utilized by working group of muscles during maximal exercise.[4,5] At maximal exercise, the majority of evidence points toward the VO2 max that is limited by oxygen supply, and cardiac output (Q) which is the major factor in determining oxygen delivery.[6] VO2 max is defined as the highest rate of oxygen consumption attainable during maximal or exhaustive exercise.

As we increase exercise intensity, oxygen consumption will eventually either plateau or decrease slightly, even with further increase in intensity, indicating we have reached the VO2 max.[3] Furthermore, research shows that VO2 max increases with physical training for only 8–12 weeks and after that this value plateaus, despite continued higher intensity training. Although VO2 max does not continue to increase, the participants continue to improve their endurance performance. Higher the percentage of VO2 max, greater the ability to perform. During endurance training, more oxygen can be delivered and consumed than in untrained state. An average increase in VO2 max of 15–20% can be observed in previously untrained males

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after training for 6 months. These improvements allow one to perform endurance activities at a higher work rate or faster pace, improving performance potential.[3]

There is a decrement in VO2 max (ml/kg/min) of about 1.6%/year in both males and females.[7] In untrained individuals, a decline in VO2 max of 5–10% per decade of life has been observed.[8]

In this study, an investigation on the effect of exercise and duration of exercise on cardiorespiratory fitness using cardiac and respiratory parameters VO2 max and endurance (fatigue index) was performed.

MATERIALS AND METHODS

After taking approval of the Institutional Ethical Committee, cardiorespiratory fitness of the sedentary healthy individuals and those healthy individuals who were involved in regular exercises in gymnasium (weight lifting exercises for the upper limbs, lower limbs, and torso along with cardio exercises) for ≤1 year and 1–5 years, respectively, was recorded in accordance with the standardized methods from May 2019 to February 2020 in a well-known local gymnasium. A complete medical history of all the subjects were recorded. Data collection was done after informed consent. Procedure of data collection was explained in detailed to subjects.

Sample Size

Total sample size = 90 males. They were grouped as follows.
Group A = Thirty healthy males regularly exercising for duration of ≤1 year.
Group B = Thirty healthy males regularly exercising for duration of 5 years.
Group C (control group) = Thirty sedentary but healthy males.

Collection of Data

VO2 MAX[9]

For estimation of VO2 max, participants were asked to perform Bruce Treadmill Test. The Bruce Protocol is a maximal exercise test, where the athlete works to complete exhaustion as the treadmill speed and incline are increased every 3 min. The length of time on the treadmill is the test score and can be used to estimate the VO2 max value.[9]

VO2 max can be predicted by ergometer more accurately as compared to other methods. In this study, metabolic equation formula available from ACSM was used to calculate VO2 max. VO2 max indirect calculations. Thus, overall, the VO2 max was calculated based on the following metabolic calculations:

Harvard step test[10]

The subjects performing the test were asked to step up and down on a platform in a cycle of 2 s. The platform is at a height of about 50 cm or 20 inches. The rate of 30 steps/min must be sustained for 5 min or until exhaustion. To ensure correct speed, a metronome was used. Exhaustion was the point at which the subject was notable to maintain the stepping rate for 15 s. On exhaustion or completion of test, the subject proceeded to sit on a chair, heartbeats were counted for 1 to 1.5, 2 to 2.5, and 3 to 3.5 min.

The results were recorded as time until exhaustion in seconds (te) and total heartbeats were counted (hb). A simple fatigue index equation was used, the formula is as mentioned below:

Fatigue index = te × 100/hb × 2
The result by above equation is rated in Table 1.

Statistical Analysis

We used descriptive statistics to access median and Inter Quartile Range of continuous characteristics among 1-year exercise, 1–5 years of exercise groups, and no exercise group.

We used to use excel and R programming software. We compared these characteristics using Kruskal–Wallis test after the data were tested normal distribution. The high VO2 max and endurance were categorized using the corresponding overall median value (including all data of three groups). High value defined if the value obtained is equal to or more than corresponding overall median value. Binary logistic regression was used to assess the association between exercise duration and VO2 max as well as the association between exercise duration and endurance. We used two-sided p value and statistical significance was evaluated at 0.05 alpha level.

RESULTS

Table 2 shows comparison between Study group A, Study group B, and Control group C with respect to age, weight, height, and body mass index.

Table 3 shows comparison between Study group A, Study group B, and Control group C with respect to VO2 max and endurance.

Table 4 shows logistic regression to assess the association between VO2 max, endurance, and exercise duration.

Table 1: Endurance or fatigue index rating for Harvard step test

Rating	Endurance (Fitness index)
Excellent	>97
Good	83–96
Average	68–82
Low average	54–67
Poor	<54

Table 2: Comparison between Study group A, Study group B, and Control group C with respect to age, weight, height, and body mass index

Characteristics	No exercise (Group C) Median, IQR *n*=30	≤1 Year exercise (Group A) Median, IQR *n*=30	1–5 Years exercise (Group B) Median, IQR *n*=30	*P*-value
Age (years)	18 (18–19)	19 (18–21)	19 (18–22)	>0.05
Weight (kg)	62.79 (53.60–71.98)	62.53 (53.59–71.47)	61.21 (52.58–69.84)	>0.05
Height (m)	1.70 (1.65–1.75)	1.70 (1.66–1.74)	1.70 (1.65–1.75)	>0.05
BMI (kg/m^2)	22.4 (21.6–23.1)	22.7 (21.7–23.5)	22.7 (22.6–22.8)	>0.05

IQR: Inter Quartile Range, N: Number of subjects, m: meters, kg: kilograms, BMI: Body Mass Index, *P*>0.05 is statistically not significant, *P*≤0.05 was considered as significant at 95% confidence interval, *P*<0.0001 was considered as highly significant

Where, high VO2 max defined as those who had VO2 max >/= 43 (median value of the overall VO2 max)

High endurance defined as those who had endurance ≥98 (median value of the overall endurance).

DISCUSSION

There is statistically significant increase in the mean of VO2 max and endurance (fatigue index) in Group B than Group A than Group C ($P < 0.0001$). $P < 0.0001$ was considered as highly significant.

There is increase in VO2 max with physical training.[3]

Mechanism

After few days of exercise, there is increase in plasma volume, which results in increased venous return. Thus, there is increase in end-diastolic volume. Along with increased end diastolic volume, there is decreased cardiac afterload which results in increased ejection fraction. Therefore, stroke volume increases.[3,11-14]

After few weeks of exercise, there is increased red blood cell volume, increased vascular function, increased capillary density, and increased mitochondrial volume density thus oxidative capacity. All these changes result in better distribution of blood to active muscle fibers and increased muscle oxygen extraction. Therefore, increased arteriovenous oxygen difference and ultimately increased VO2 max.[3,11-14]

Whereas after few months of exercise, there is increased ventricular compliance and ventricular hypertrophy. This causes increased end-diastolic volume and finally VO2 max increases.[3,11-14]

According to Fick's equation[15]

VO2 max = SV × HR × (a – vO2 difference)

Where,
SV is stroke volume

Table 3: Comparison between Study group A, Study group B, and Control group C with respect to VO2 max and endurance

Parameters	No exercise Group C	≤1 Year exercise Group A	1–5 years exercise Group B	P-value
VO2 Max				
Median	37	43	59	0.0001*
IQR	(36–39)	(41–45)	(46–61)	
Endurance				
Median	96	98	99	0.0001*
IQR	(95–98)	(96–98)	(98–100)	

**P*<0.0001 was considered as highly significant

Table 4: Logistic regression to assess the association between VO2 max, endurance, and exercise duration

Parameters	No exercise Group C	≤1 Year exercise Group A	1–5 Years exercise Group B
VO2 Max			
High VO2 Max	2 (7%)	17 (57%)	28 (98%)
OR 95% C.I.	Ref	18.3 (3.96 – 91.2)	196 (26 – 1490)
P value	-	<0.0001	<0.0001
Endurance (Fatigue index)			
High endurance	8 (26%)	15 (50%)	24 (80%)
OR 95% C.I.	Ref	2.75 (0.93–8.10)	11 (3.29–36.75)
P value	Ref	0.07	<0.0001

High VO_2 max: Defined as those who had VO_2 Max >/= 43 (Median value of the overall VO_2 Max). High endurance: Defined as those who had endurance >= 98 (Median value of the overall endurance)

HR is heart rate
(a – vO2 difference) is arteriovenous oxygen difference

Endurance (Fatigue Index)

Physical training results in increase in endurance.[3]

Mechanism

Increased level of anaerobic substrates, that are – Adenosine triphosphate, Phosphocreatine, free creatine, and glycogen.[3,16-18]

Increase in endurance is due to increased level of anaerobic substrates (adenosine triphosphate, phosphocreatine, free

creatine and glycogen), increased activity of key enzymes that control the glycolytic (anaerobic) phase of glucose catabolism and motivation which leads to improved pain tolerance.[3,16-18]

CONCLUSION

In the present study, we found that there is statistically significant improvement in VO2 max and endurance (fatigue index) in ≤1-year exercise group compared to the no exercise group, whereas there is profound improvement in VO2 max and endurance (fatigue index) in 1–5 years exercise group compared to 1-year exercise group. This, thus, shows a positive correlation between duration of exercise and improvement of cardiorespiratory parameters.

It is therefore advisable to make exercise as a part of lifestyle. Thus regular, long-term exercise routines are recommended for a healthy and quality life.

Limitations of the Study

The sample size is less so results can differ in larger population. Experiments with different intensities of cardio exercises were not performed. The reliance on self-reported data for physical training could be influenced by poor recall which may be another limitation of this study. Only males were part of the study.

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Original Article

A Descriptive Analytical Research on Diagnostic and Prognostic Immunohistochemical p-16/ki67 Staining and Colposcopy Imaging, Cancer Pharmacotherapeutics, Immunotherapeutics, and co-therapeutic Modalities in Cervical Malignancy: A Medical Book

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Abstract

The diagnosis, imaging, and prognosis of cervical malignancy and the pre-cancer can be performed with human papilloma virus (HPV) DNA testing and p-16/Ki67 immunohistochemical staining, other than the Papanicolaou test, and the subsequent colposcopy. HPV-associated cancers are typical epithelial malignancies that are difficult to treat when metastatic. Chemotherapy generally consists of combinations of cytotoxic agents, often administered in conjunction with a biological agent. These regimens have limited clinical activity and substantial toxicity, and better treatments are needed. Immunotherapy works through different mechanisms than chemotherapy and has been a breakthrough for the treatment of certain malignancies. Targeting HPV oncoproteins with antigen-specific immunotherapy using therapeutic vaccines are under clinical trials for cervical cancer and metastatic disease treatment. Immunotherapy with PD-1–targeted agents has shown clinical activity in genitourinary and oropharyngeal cancers. This descriptive analytical research study explores cervical malignancy, and the different aspects of diagnostic p-16/Ki67 immunostaining, colposcopy imaging, cancer pharmacotherapeutics, onco-immuno-therapeutics and co-therapeutic modalities for a comprehensive cervical cancer treatment.

Key words: Immunohistochemistry, Colposcopy, Cancer Pharmacotherapeutics, Immunotherapeutics, Bevacizumab, Ipilimumab, Cemiplimab, Pembrolizumab, Preventive Human papilloma virus vaccines, GX-188E therapeutic DNA vaccine, Axalimogene filolisbac, Adoptive T-cell therapy

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INTRODUCTION

According to GLOBOCAN 2018, cervical cancer is the fourth most commonly diagnosed tumor and the fourth cause of cancer death in females, worldwide, but ranks second in both incidence and mortality in the lower income countries. The diagnosis, imaging, and prognosis of

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cervical malignancy and the pre-cancer can be performed with human papilloma virus (HPV) DNA testing and p-16/Ki67 immunohistochemical staining, other than the Papanicolaou test, and the subsequent colposcopy. HPV-associated cancers are typical epithelial malignancies that are difficult to treat when metastatic. Chemotherapy generally consists of combinations of cytotoxic agents, often administered in conjunction with a biological agent. These regimens have limited clinical activity and substantial toxicity, and better treatments are needed. Immunotherapy works through different mechanisms than chemotherapy and has been a breakthrough for the treatment of certain malignancies. Targeting HPV oncoproteins with antigen-specific immunotherapy using therapeutic vaccines are under clinical trials for cervical cancer and metastatic disease treatment. Immunotherapy with PD-1–targeted agents has shown clinical activity in genitourinary and oropharyngeal cancers.

Objective

The objective of this descriptive analytical research study was to explore cervical malignancy, and the different aspects of diagnostic colposcopy, cancer pharmacotherapeutics, onco-immuno-therapeutics, and co-therapeutic modalities for a comprehensive cervical cancer treatment.

METHODOLOGIES, RESULTS, AND DISCUSSION

A Descriptive Analytical Research Study

p16/Ki-67 immunostaining to detect cervical cancer precursors among colposcopy referrals

Cytology-based screening has limited sensitivity to detect prevalent cervical precancers. HPV DNA testing is highly sensitive and provides a high, long-term reassurance of the low risk of cervical cancer. The specificity of HPV DNA testing is limited, requiring more disease-specific markers for efficient screening approaches. In one study, liquid-based cytology samples were collected from 625 women referred to colposcopy. A slide was stained using the CIN tec plus cytology assay. Pap cytology and HPV genotyping were conducted from the same vial. Clinical performance characteristics were calculated for all women, stratified by age, and for women referred with a low-grade squamous intraepithelial lesion (LSIL) Pap. In this study, p16/Ki-67 positivity increased with histologic severity, from 26.8% in normal histology, 46.5% in CIN1, and 82.8% in CIN2 to 92.8% in CIN3. Among women with CIN3, p16/Ki-67 positivity increased from 77.8% for women younger than 30 years without HPV16 to 100% for women 30 years and older with HPV16. The sensitivity and specificity to detect CIN3 were 93.2% and 46.1%, respectively, and increased to 97.2% and 60.0% among women 30 years and older. In women with high-risk (HR)-HPV–positive atypical squamous cells of undetermined significance (ASC-US) and LSIL, sensitivity and specificity for detection of CIN3 were 90.6% and 48.6%, respectively. This study concluded that p16/Ki-67 testing could reduce referral to colposcopy by almost half while detecting the most severe cases of CIN3. The high sensitivity of p16/Ki-67 with significantly improved specificity compared with HPV testing makes p16/Ki-67 a viable option for LSIL triage.

Cervical Pap smear screening has led to a substantial reduction of cervical cancer incidence in countries with established screening programs. However, Pap cytology has limited reproducibility, and a single Pap test has limited sensitivity to detect cervical precancer. HPV DNA testing is highly sensitive and provides a high, long-term reassurance of low risk of cervical cancer among women testing negative, permitting safe extension of screening intervals. Recently, more disease-specific molecular markers of cervical cancer have been recognized that may provide a combination of high sensitivity and high specificity for detecting cervical precancer. Most of these markers have been identified on the basis of our understanding of HPV related carcinogenesis. The progression from HPV infection to cervical precancer is characterized by a substantial change in the viral gene expression, from a transient infection characterized by expression of structural genes to a transforming infection with strong expression of viral oncogenes that interfere with host cell-cycle control. The expression of several host genes is affected by the oncogene products of HPV, including those involved in cellular proliferation, such as Ki-67, and cell-cycle control, such as p16. Immunostaining for p16 has been determined to be an effective biomarker of cervical disease in histology and cytology specimens. It is widely used to improve the reproducibility of cervical biopsy interpretations. In cytology, p16 can improve the accuracy for detecting cervical precancer compared with conventional cytology. Recently, a double-label immunostain for p16 and Ki-67 was developed that allows recognition of abnormal cells simply based on co-staining of the two markers in the same cell, potentially obviating the need for morphologic interpretation.

In a large U.S.-based colposcopy referral population with excellent disease ascertainment, it was shown that cytologic staining for p16/Ki-67 has comparable sensitivity, but significantly higher specificity than HPV DNA testing, potentially reducing colposcopy referral by half. It was shown that p16/Ki-67 does best at detecting precancers with the highest risk of progression to cancer, namely, those related to HPV16 among women 30 years and older. These data from a large, independent study suggest that p16/

Ki-67 can be an important component of new HPV-based screening strategies.

Oncological Diagnostic Applications of Colposcopy

Colposcopy is a diagnostic procedure performed to evaluate women with an abnormal Papanicolaou (Pap) test, women with visual inspection with acetic acid, women positive for high-risk human papillomavirus (HPV) DNA, or with a suspicious appearing cervix even if the Pap test is normal. Women with LSIL and HPV-positive ASC-US are uniformly referred to colposcopy. All women with an LSIL referral Pap and an HPV-positive ASC-US referral Pap are usually evaluated by colposcopy and biopsy, for an analysis of the performance of p16/Ki-67 for triage of these cytology categories. Colposcopy is also performed as a post-treatment follow-up of intraepithelial and invasive carcinoma. Colposcopy is a procedure in which a lighted, magnifying instrument called a colposcope is used to examine the cervix, vagina, and vulva. It is a diagnostic procedure performed to evaluate abnormal cytology results from a screening Pap test. It is well known that colposcopy has significant variability and poor reliability between colposcopists. The ASCCP (American Society for Colposcopy and Cervical Pathology) published colposcopy standards in 2017 to address these concerns related to colposcopy. Colposcopy is a procedure in which a lighted, magnifying instrument called a colposcope is used to examine the cervix, vagina, and vulva. It is a diagnostic procedure performed to evaluate abnormal cytology results from a screening Pap test.

The indications for colposcopy include evaluation of women with an abnormal Pap test to localize the lesion, to map out the extent of the lesion, to select the biopsy site or sites; women positive for high-risk HPV DNA; visual inspection with acetic acid positive women, suspicious appearing cervix, postcoital or postmenopausal bleeding, even if the Pap smear is normal; unexplained abnormal lower genital tract bleeding; persistent inflammatory or unsatisfactory cervical cytology despite appropriate treatment, especially with high-risk factors for carcinoma cervix; persistent abnormal vaginal discharge or pruritus vulvae; for the identification and management of subclinical papillomavirus infection; patients with history of *in utero* diethylstilbestrol (DES) exposure; for the conservative management of intraepithelial neoplasia; identification and management of vaginal extension of cervical neoplasia; and for post-treatment follow-up after treatment of intraepithelial and invasive carcinoma and post-irradiation follow-up.

The ASCCP (American Society for Colposcopy and Cervical Pathology) has published standardization guidelines for the performance of colposcopy. The ASCCP makes recommendations for extensive and minimum requirements for a colposcopy. The colposcopist should examine the vulva, vagina, and cervix grossly in the natural state and also after the application of 5% acetic acid. The entire cervix and squamocolumnar junction must be visualized for adequacy. Both white light and a red-free (blue or green) filter should be applied to the visual field to identify any lesion.

Directed biopsies of lesions should be taken of each abnormal finding. Documentation in a minimum of text format should comment on the visibility extent, size, location, and description of each lesion (color, contour, border, and vascular changes), presence or absence of acetowhitening, complete or incomplete visibility of the squamocolumnar junction, documentation of biopsies and locations, if an endocervical curettage was performed, and finally the impression of the colposcopy (benign-normal, low grade, high grade, or cancer). Application of Monsel's solution or silver nitrate should be applied after the colposcopy is completed, and all biopsies are taken. Grade of cytological abnormality, colposcopic adequacy, visibility, and type of squamocolumnar junction should be documented. The location of lesion, size, and extent of lesion, endocervical, or vaginal extension of the lesion should also be clearly documented. Abnormal colposcopic findings should be described location wise in detail, and colposcopic impression should be made in terms of low grade or high-grade lesion along with Reid's or Swede score. Histopathologic diagnosis should never be made on colposcopy only. According to the 2011 IFCPC Nomenclature, the Swede score is used to score the colposcopic findings and to have uniformity in the reporting system. The total score is 10. Colposcopy is a diagnostic procedure done due to an abnormal cervical screening test or a visible lesion seen on the cervix during an examination. This diagnostic procedure assists with the formulation of a management plan based on the results of the biopsied pathology or lack of results. In general, all results can either be observed or treated and are based on evidence-based guidelines. Low-grade lesions can be followed up and managed according to ASCCP guideline algorithms. High-grade lesions are treated depending on the patient's age and fertility status. A patient that is pregnant will have their treatment deferred until after delivery unless there is a specific concern for an invasive lesion. Invasive lesions should be referred to an obstetrician and gynecologist and a gynecological oncologist for treatment options.

The general assessment is performed to determine whether there is adequacy or inadequacy for the reason (e.g., cervix obscured by inflammation, bleeding, and scar); to visualize the squamocolumnar junction and to determine whether

the visibility is completely visible, partially visible, or not visible; and also to visualize the transformation zone types 1, 2 and 3.

The colposcopy is performed to distinguish between normal and abnormal colposcopic cervical findings, which include the visualization of whether the original squamous epithelium is mature, columnar epithelium is atrophic or not, whether there is ectopy, metaplastic squamous epithelium, nabothian cysts, or crypt gland openings.

For visualizing abnormal colposcopic findings, the general characteristic features are looked into. The location of the lesion is observed, whether it is inside or outside the T-zone. The location of the lesion is also observed according to the clock position. The size of the lesion is examined, along with the number of cervical quadrants the lesion covers and size of the lesion in the percentage of the cervix. The grading of the lesion is done as follows: in grade 1, minor lesions, there would be thin aceto-white epithelium, irregular, geographic border, fine mosaic and fine punctation; in grade 2, major lesions, there would be dense aceto-white epithelium, rapid appearance of aceto-whitening, cuffed crypt (gland) openings, coarse mosaic, coarse punctuation, sharp border, inner border sign and ridge sign; in non-specific lesions, there would be leukoplakia (keratosis and hyperkeratosis), and erosion, Lugol's staining (Schiller's test) is done to observe whether the tissues are stained or non-stained. If the lesion is suspicious for invasion, there might be the presence of atypical vessels, or associated signs, such as, fragile vessels, irregular surface, exophytic lesion, necrosis, ulceration (necrotic), tumor, or gross neoplasm. Furthermore, miscellaneous findings might be seen in congenital transformation zone, condyloma, polyp (ectocervical or endocervical), inflammation, stenosis, congenital anomaly, post-treatment consequence, and endometriosis.

The scoring is done as follows:

Score	0	1	2
Aceto uptake	Zero or transparent	Shady, Milky (not transparent; not opaque)	Distinct, opaque white
Margins or surface	Diffuse	Sharp but irregular, jagged, 'geographical' satellites	Sharp and even, the difference in surface level, including 'cuffing'
Vessels	Fine, regular	Absent	Coarse or atypical
Lesion size	<5 mm	<5 mm 5–15 mm or 2 quadrants	>15 mm or 3–4 quadrants/ endocervical undefined
Iodine staining	Brown	Faintly or patchy yellow	Distinct yellow

Overall Swede Score

Overall Swede score	Colposcopic prediction of probable histology
0–4	Low grade/normal CIN 1
5–6	High grade/non-invasive cancer CIN 2+
7–10	High grade/suspected invasive cancer CIN 2+

Human Papillomavirus Associated Malignancies and Therapeutics

Human papillomavirus (HPV)-associated cancers are common epithelial malignancies that account for approximately 5% of all cancers worldwide. They occur at varied genitourinary and oropharyngeal anatomic sites. Advanced-stage HPV-associated cancers are difficult to treat. Advanced-inoperable cervical cancer is a challenging entity due to increased percentage of locoregional and distant recurrences. Recurrent cervical cancer not amenable to radical treatment, as well as metastatic disease, is difficult to cure, with a bad prognosis.

Minimally invasive robotic surgery has become an effective surgical technique for the treatment of gynecologic malignancies, like cervical cancer. Minimally invasive surgery (MIS) is the standard approach to performance of several gynecologic procedures including hysterectomy, gynecologic cancer staging procedures, myomectomy, pelvic organs prolapse repair, and select adnexal procedures. Robotic-assisted surgery, a computer-based MIS approach has been adopted widely in the United States and several other countries.

As for the pharmacotherapeutic modalities of cervical cancer treatment, the approved immune-checkpoint inhibitors, the "first generation," include monoclonal antibodies directed against PD-1 (pembrolizumab, nivolumab, and cemiplimab); against PD-L1 (atezolizumab, avelumab, and durvalumab); and against protein CTLA-4 (ipilimumab). Combination chemotherapy and bevacizumab offers some clinical benefit, and anti-programmed death 1 receptor (PD-1) therapy has shown clinical activity, but these malignancies generally are incurable and better treatments are needed. Sequential ipilimumab after chemoradiotherapy is given in curative-intent treatment of patients with node-positive cervical cancer. Anti-tumor activity of cemiplimab as monotherapy or in combination with hypofractionated radiation therapy is given in patients with recurrent or metastatic cervical cancer. Pembrolizumab and GX-188E therapeutic DNA vaccine are also emerging cervical cancer treatment options in patients with HPV-16-positive or HPV-18-positive advanced cervical cancer. Pembrolizumab, an IgG4-kappa humanized monoclonal antibody, against the programmed

cell death protein 1 (PD-1) receptor, has been approved for the treatment of recurrent or metastatic cervical cancer. Although immune-checkpoint blockade therapy is rapidly altering the treatment landscape in solid tumors, the efficacy of immune-checkpoint blockade therapy with antibodies directed against CTLA-4, PD-1, and PDL-1 in advanced gynecologic cancers has been limited. The exception has been the PD-1 inhibitor pembrolizumab in microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) advanced endometrial cancers, highlighted by the recent conditional approval of pembrolizumab in recurrent or metastatic PDL-1 positive cervical cancers and the accelerated approval of pembrolizumab and lenvatinib in microsatellite stable (MSS) or mismatch-repair proficient (pMMR) advanced endometrial cancer. GX-188E vaccination has been shown to induce human papillomavirus (HPV) E6-specific and E7-specific T-cell responses and cervical lesion regression in patients with cervical precancer. Preventive HPV vaccines and adoptive T-cell therapy, the systemic infusion of therapeutic T cells, are potential emerging cancer treatment modalities. Cellular therapy has shown to mediate the regression of HPV-associated cervical cancer, oropharyngeal cancer, and anal cancer, including durable and complete regression of cervical cancer.

The currently recommended standard of care treatment of cervical malignancy, according to the respective FIGO staging is that, for FIGO Stages IA1 and IA2, type II radical hysterectomy and pelvic lymph node dissection is suggested; for Stages IB1 and IIA1, type III radical hysterectomy and pelvic lymph node dissection are suggested; for Stages IB2 and IIA2, pelvic external beam radiation therapy, brachytherapy, and cisplatin based concurrent chemotherapy are suggested; for Stages IIB and IVA, pelvic external beam radiation therapy, with brachytherapy and cisplatin-based concurrent chemotherapy, and with or without external beam radiation therapy to para-aortic nodes are suggested; and for stages IVB or recurrent disease not amenable to local therapy, paclitaxel, cisplatin and bevacizumab, or, paclitaxel and cisplatin, or, paclitaxel, topotecan and bevacizumab, or, paclitaxel and topotecan, or, paclitaxel and carboplatin, are suggested.

Targeted Therapy in Cervical Cancer

Antiangiogenic therapy targeting the vascular endothelial growth factor (VEGF) and other pathways has improved outcomes in multiple solid tumors. Poor prognosis and early recurrence in cervical cancer have been associated with VEGF expression. Bevacizumab is a recombinant humanized monoclonal immunoglobulin (Ig)-G1 antibody directed against VEGF-A. By inactivating VEGF-A, it blocks signal transduction through VEGFR-1-associated and VEGFR-2-associated pathways. The other targeted therapies, under various phases of clinical trials, include tyrosine kinase inhibitors sunitinib, which inhibits VEGFR, PDGFR, c-KIT, and FLT-3, and pazopanib, which inhibits VGFR, PDGFR, and c-KIT. Brivanib, an inhibitor of VEGFR and FGFR, is also another targeted therapy modality of advanced cervical cancer, which is under clinical trial. Other VEGF/VEGFR targeting drugs, such as, nintedanib and cediranib are also investigational drugs. Cervical cancer expresses moderate to high levels of epidermal growth factor receptor (EGFR) protein. Several studies with EGFR-targeted therapies, gefitinib, erlotinib, and cetuximab, are undergoing different phases of clinical trials. Different clinical trials were also conducted with lapatinib, a HER2 inhibitor, and pazopanib (combination of HER2 inhibitor with VEGFR inhibitor). A recent study of molecular profiling of cervical cancer samples and testing in patient-derived xenograft (PDX) models has demonstrated that co-administration of trastuzumab and lapatinib, the BCAR4, breast cancer anti-estrogen resistance four amplification or HER2-overexpressed drugs in PDX significantly inhibited tumor growth compared with the control. A mTOR targeting drug, such as temsirolimus, and histone deacetylase (HDAC) targeting drug, like valproic acid, are also under investigational phase.

PD-1 (programmed cell death 1) and PD-L1 expression on cervical cancer infiltrating T cells and dendritic cells, respectively, has been reported to be associated with high risk HPV positivity and increasing cervical intraepithelial neoplasia grade. PD-1 is expressed by a high fraction of infiltrating CD8 T cells in cervical cancer, suggesting that blocking of PD-1, by the immune checkpoint inhibitors, such as pembrolizumab and ipilimumab, might have therapeutic potential and is undergoing clinical trials. Nivolumab, a fully human antibody against PD-1, is also undergoing different clinical trials as a second-line treatment of cervical cancer. PARP inhibitors, suhc as, olaparib and veliparib, are also being investigated for a potential anti-carcinomatous drug target. Poly (ADP-ribose) polymerase (PARP) is a constitutively expressed enzyme that is involved in base excision DNA repair as well as cell replication, transcription, differentiation and gene regulation, and its inhibition has been shown to be synthetic lethal with homologous recombination DNA repair defects. The PARP inhibitor veliparib was studied in combination with cytotoxic therapy in women with recurrent or persistent cervical cancer after receiving pelvic radiation, with or without cisplatin.

The immune checkpoint inhibitor approach is likely to provide higher benefit in earlier lines of treatment and perhaps in combination with other strategies such as chemotherapy and/or radiotherapy.

Immunotherapeutics of Cervical Carcinoma

The rationale for immunotherapy in cervical carcinoma (CC) is that, given that almost all CCs are human papillomavirus (HPV)-related tumors, CC could represent a paradigmatic example for the benefit obtained from immunotherapy. The immune system is often stimulated by non-human (viral) antigens, and for this reason it was possible to develop a vaccine as tumor prophylaxis. Several studies have confirmed that a large number of genomic alterations are found in CC patients, for example, in the following genes: KRAS, PIK3CA, TP53, and PTEN. This high mutational burden might be responsive to immunotherapy. HPV-integrated genes are often described in CCs.

In a pharmacogenomic study, it was identified that 384 integrated gene sites could influence T cell activation in the KEGG (Kyoto Encyclopedia of Genes and Genomes, https://www.genome.jp/kegg/) database, indicating the possibility of a strong correlation between HPV infection and immune surveillance. There is an interesting correlation between HPV-mediated immune tolerance and tumor development. The ability of HPV to promote a so-called "non-lytic life cycle" inactivates (or partially activates) dendritic cell migration to lymph nodes and consequently inhibits immune activation. At the same time, low expression of E6 and E7 HPV proteins reduces Langerhans cell activity, leading to an immune-tolerant status that can potentially promote CC development. With regard to immune checkpoints, high levels of CTLA4 and PD1/PD-L1 are often detected in CC patients, and PD1/PD-L1 are frequently expressed in dendritic cells in Cervical Intraepithelial Neoplasia (CIN) samples. PD1/PD-L1 expression has been shown to be present in 95% of intraepithelial lesions and around 80% of squamous carcinomas. Several studies on CC have demonstrated high expression levels of immune-suppressive cytokines, such as IL-10, confirming an interesting link between immune checkpoints and CC progression. Recently, it was shown that PD-L1 expression correlates with TILs, predicting response in CC patients treated with neoadjuvant chemotherapy.

One antibody–drug conjugate, tisotumab–vedotin, has been studied in cervical cancer patients.

The immunotherapeutic modalities of cervical cancer treatment include the following:

a) Prophylactic
   (i) Preventive HPV vaccines
b) Therapeutic
   (i) GX-188E therapeutic DNA vaccine
   (ii) Axalimogene filolisbac ADXS11-001
   (iii) Adoptive T-cell therapy

Cervical cancer therapeutic vaccines aim to eradicate HPV-infected cells by stimulating cytotoxic T cells against the viral/tumor antigens. The HPV E6 and E7 oncoproteins are expressed in HPV-associated cancers and are ideal targets for a therapeutic vaccine. Many live bacterial vectors have been explored in HPV therapeutic vaccines including *Listeria monocytogenes*, *Lactobacillus lactis*, *Lactobacillus plantarum*, *Salmonella enterica,* and BCG. *Listeria monocytogenes* has the ability to replicate in the cytosol of antigen-presenting cells and infects monocytes and macrophages, allowing bacterial peptide antigens to be processed and presented through both Major Histocompatibility Complex Classes I and II pathways, generating potent CD8 and CD4 T cell–mediated immune responses. The sensitivity of *Listeria* to antibiotics allows the vector to be killed *in vivo* as required. The *Listeria*-based vaccine potency is further enhanced by encoding recombinant proteins composed of HPV E6 and E7 antigens fused to immunostimulatory molecules. Axalimogene filolisbac (ADXS11-001), a live, attenuated *Listeria monocytogenes* bacterial vector secreting HPV-16 E7 fused to listeriolysin O (LLO), is under investigation for treatment of HPV-associated malignancies including cervical cancer. A phase II study evaluated the safety and efficacy of ADXS11-001, administered with or without cisplatin, in patients with recurrent or refractory cervical cancer following prior chemotherapy and/or radiotherapy.

Therapeutic T cells, is an emerging cancer treatment modality that can induce complete tumor responses in some patients with B-cell malignancies or metastatic melanoma. A study was conducted to test whether adoptive T-Cell therapy could mediate the regression of HPV-associated epithelial cancers. A method was established in the study to generate independent tumor-infiltrating lymphocyte (TIL) cultures from fragments of a resected metastatic tumor deposit. Because HPV-associated cancers constitutively expressed the HPV E6 and E7 oncoproteins, immunologically foreign viral proteins that are attractive targets for immunotherapy and cultures with HPV-oncoprotein reactivity were selected preferentially for administration to patients. A completed clinical trial was presented with long-term follow-up, in which, 18 patients with metastatic cervical cancer and 11 patients with other cancers participated. The trial was a Phase II design with two cohorts, cervical cancers and noncervical cancers. Cell infusion was preceded by a lymphocyte-depleting conditioning regimen and followed by systemic high-dose aldesleukin. Tumor responses occurred in 5 of 18 (28%) patients in the cervical cancer cohort and 2 of 11 (18%) patients in the noncervical cancer cohort. Two of the responses in cervical cancer were complete and the ongoing treatment continued for 67 and 53 months follow-up. Responses

in the noncervical cancer cohort were in anal cancer and oropharyngeal cancer. The HPV reactivity of the infused T cells correlated with clinical response. Peripheral blood repopulation with HPV-reactive T cells also correlated with clinical response. These findings supported the concept that cellular therapy can mediate the regression of epithelial cancers, and they suggested the importance of predictive biomarkers and novel treatment platforms for more effective therapies.

In another similar study on the target antigens in two patients, complete responses were experienced in the clinical trial. Tumor-infiltrating lymphocyte therapy was administered to each patient, which targeted HPV antigens. However, the predominant target antigens were a cancer germline antigen in one patient and mutant neoantigens in another patient.

A number of biological agents modulating different signal transduction pathways are currently in clinical development, such as cell cycle inhibitors, histone deacetylases, cyclooxygenase-2 (COX-2), mammalian target of rapamycin (mTOR), heat shock protein (HSP), WEE1, NOTCH signaling, and others. With a better understanding of the central role of HPV infection in tumorigenesis of cervical cancer, more studies are evaluating the role of immune-directed therapies in cervical cancer, in adjuvant as well as metastatic settings.[1-16]

CONCLUSION

Therefore, this descriptive analytical research on cervical malignancy, diagnostic colposcopy, cancer pharmacotherapeutics, immunotherapeutics and co-therapeutic modalities, well-delineates a detailed diagnostic colposcopy, cancer pharmacotherapeutics, immunotherapeutics, and co-therapeutic modalities. This study would certainly remain a landmark on the way toward future innovations in newer drug discovery and development of more appropriate, efficacious, safe, high quality, easily accessible, inexpensive, easily administered and comprehensively suitable drug, for a much better pharmacotherapy and immunotherapy of cervical malignancy, along with the other therapeutic modalities.

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Original Article

Assessment of Cognitive Function Status in Chronic Obstructive Pulmonary Disease and Its Association with Understanding Inhaler Technique

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a treatable disorder wherein technique of inhalational medication plays a major role in adequate management of the patients in which cognitive impairment may have an adverse effect.

Materials and Methods: A descriptive study was conducted among 150 COPD patients attending chest clinic and medicine OPD in University College of Medical Sciences, GTB hospital, Delhi to assess the cognitive function status in COPD and its association with the ability to understand the inhaler technique.

Results: The mean age of the study group 54.52 ± 5.99 with 18.7% (28) females and 81.3% males. About 7.3% were having diabetes, 7.3% were being treated for hypertension, 2.7% had a history of stroke, 16.0% had asthma, and 1.3% were currently being treated for tuberculosis. About 94% did not have a graduation degree. About 82.7% patients out of 150 were using an inhaler. The inhaler demonstration was seen in only 20% (30) of the participants. An average Montreal cognitive assessment score was 19.73 ± 2.55. About 92.7% patients had score <26. The total score for correctly using the inhaler technique was 6.78 ± 0.77 at baseline and 6.01 ± 0.79 after a follow-up period of 15 days. An error in at least one step of the inhalation technique was seen in 96.7% of participants. There was statistical significant association (P = 0.003) of MOCA with increase in age.

Conclusion: Cognitive dysfunction should be part of the routine diagnostic procedures in COPD patients to grade the overall impact of patients' respiratory conditions and to decide the most effective therapeutic actions and strategies.

Key words: Chronic obstructive pulmonary diseases, Inhaler technique, MOCA, Montreal cognitive assessment

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an important public health challenge that is both preventable and treatable. By the year 2030, it is expected that it will be the third leading cause of death from the current status of the fifth.[1] According to estimates from the Global Burden of Disease Study, COPD was prevalent in more than 300 million people in 2013. In European adult populations over 40 years, the prevalence of COPD ranges between 15–20% and is higher in men than in women.[2]

The main risk factor for the development of COPD is tobacco smoking but only around 20% of smokers develop the disease. The other risk factors contributing to increased risk of this disease are indoor and outdoor air pollution,[3] occupational exposure, second-hand smoke, genetic factors, lung growth, and development. Socioeconomic status, age, and sex are the other factors that are also related to the development of COPD.

Mild cognitive impairment refers to impairment in cognition above that which is seen with normal age-related cognitive decline, but not severe enough to cause significantly impaired daily function.[4] The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V) classifies MCI as a "mild neurocognitive disorder," and specifies that there must be

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both a subjective and objective decline from the previous level of functioning in one or more of the six cognitive domains, not substantially interfering with instrumental activities of daily living, and not occurring in the context of delirium or other psychological disorders.[5] The mechanism proposed for cognitive impairment in patients of COPD is neuronal damage mediated by hypoxia as a result of pulmonary disease or the comorbidities or risk factors that adversely affect the brain. Mayo Clinic Study of Ageing has demonstrated that patients of COPD have increased the risk of mild cognitive impairment. The various other screening tests that are being used for the cognitive impairment are Mini-Mental State Examination (MMSE), Functional Activities Questionnaire, NIH Toolbox Cognition Batteries, and AD8 Dementia Screening Interview, Memory Impairment Screen (MIS), Animal Naming, General Practitioner Assessment of Cognition Screening Test (CPCoG), The Saint Louis University Mental Status (SLUMS) Examination, and MiniCog.[6]

Inhaled medications play a key role in the treatment of COPD. This method of application has the advantage to deliver the drug directly into the airways. Therefore, high local concentrations can be achieved with a reduced risk of systemic side effects. Different sequential steps are necessary to achieve the correct application of these devices. Incorrect performance of one or more steps can substantially reduce the delivery of the administrated substance and consequently the effectiveness and safety of the medication. Various studies have shown that 50–80% of the investigated patients do not use their inhaler devices correctly.[7]

Cognitive impairment may have a bearing on the technique of inhalation.[8] This study was conducted to assess the cognitive function status in COPD and its association with the ability to understand the inhaler technique at an outpatient clinic of a tertiary care hospital.

MATERIALS AND METHODS

Study Site

The study was conducted at the Department of Medicine, UCMS and GTB Hospital, Delhi.

Study Design

It was a descriptive study.

Study Duration

The study duration wasSeptember 2018–April 2020.

Study Participants

Inclusion criteria

The following criteria were included in the study:

- Diagnosed cases of COPD as per GOLD Staging I, II, and III.
- Age: 40–60years
- Literate (As per Census, a person aged seven and above who can both read and write with understanding in any language, is treated as literate).

Exclusion criteria

The following criteria were excluded from the study:

- Patients presenting with acute exacerbation of COPD
- History of head injury, brain tumors, epilepsy, and dementia
- History of neurological or neuropsychiatric symptoms
- Use of sedatives and antipsychotics
- Any visual or hearing impairment.

Methodology

Following approval from the Institutional Ethics Committee (IEC), 150 patients were recruited serially in the Chest and Medicine OPD of UCMS and GTB Hospital. These patients were then subjected to undergo pulmonary function tests and were classified as per GOLD Staging I, II, and III. Among these, patients fulfilling inclusion and exclusion criteria were taken as the study population.

These diagnosed cases of COPD were then subjected to detailed history. The history included demographic data for age, literacy, and occupation. History was obtained relating to the duration of COPD and the use of an inhaler, exposure to industrial smoke, pollution, smoking, comorbid conditions, and previous or current history of pulmonary tuberculosis or any other lower respiratory tract infection. The participants were enquired in detail about the use of inhalers if any previous demonstration has been given regarding its use, previous pulmonary function tests if any, and drugs they were taking for COPD. The patients were also enquired about any previous psychiatric conditions, addictions such as alcohol, smoking, tobacco chewing, and any history of stroke or brain injury in the past. The participants were asked about the most common presenting symptom that they were having at the time of presentation to the hospital. The clinical examination incorporated the measurement of physical parameters such as height, weight, blood pressure (both systolic and diastolic), clinical signs such as clubbing, lymphadenopathy, pallor, edema, and icterus. The respiratory system was examined to look for any significant findings. The chest X-ray was also examined to look for the common findings among different participants of COPD.

Five milliliters of blood were withdrawn from the patients with their due consent for routine investigation (Liver function tests, Kidney function tests, complete blood counts, and blood Sugar) to rule out coexisting comorbidities which may, later on, confound the cognitive assessment.

At the first visit after clinical examination patients were given complete demonstration and training to use pressurized metered-dose inhalers using ten steps of inhaler technique given by National Asthma Council Australia.[9] The subjects were then asked to repeat these ten steps of inhaler technique after an interval of 5 min and scores were given as ´1´ for each correctly performed step and ´0´ for incorrectly performed step. Inhaler technique scoring was based on the number of steps performed correctly out of 10.

During this same visit, patients were assessed for cognitive function using Montreal Cognitive Assessment scoring using MOCA Hindi Version. MOCA is a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. There are eight domains and each domain was tested among the study participants using the Hindi version of MOCA. The total possible score is 30 points; a score of 26 or above is considered normal.[10]

All the subjects were then followed by a gap of 15 days for the inhaler technique and were again asked to repeat ten steps of inhaler technique and were given scores out of ten. At the follow-up visit difference in the score from the baseline score was also obtained. The inhaler technique score was then compared with the MOCA score to assess cognitive function and its association with an understanding of the inhaler technique.

Data Management and Statistical Analysis

Statistical analysis

Data were entered into MS Excel and cleaned. SPSS 20.0 Software has been used for statistical analysis. Categorical value like cognitive status impairment, gender, and so on was presented as a proportion. Continuous variables such as MOCA (Montreal Cognitive Assessment) scoring, inhaler technique scoring, and age etcetera were presented as a mean and standard deviation.

The continuous variables such as inhaler technique score, and age etcetera were compared in the two groups, that is, MOCA <26 and MOCA >26 by Student's t-test. The categorical variables such as gender were compared using the Chi-square test. $P < 0.05$ was considered statistically significant.

Ethical Consideration

Approval from the Institutional Ethical Committee of UCMS was taken for conducting the study. Informed written consent was taken from the patients.

RESULTS

The total number of patients who participated in the study was 150. The age of the participants ranged from 40 to 60 years. The mean age of the study group was 54.52 ± 5.99. There were 18.7% (28) females and 81.3% (122) males. Among all the study participants cough and shortness of breath were the most common symptoms 79.3% (119) followed by chest pain 41.3% (62) and palpitations 8% (12). 20 (30%) had pulmonary TB at presentation or had taken treatment for it in the past. About 4.7% (7) had lower respiratory tract infection at presentation.

About 7.3% (11) were having diabetes, 7.3% (11) were being treated for hypertension, 2.7% (4) had a history of stroke, 16.0% (24) had asthma, and 1.3% (2) were currently being treated for TB. About 74.7% (112) had a history of exposure to biomass fuel, 19.3% (29) had exposure to industrial smoke, and 3.3% (5) had increased exposure to air pollution. About 68% (102) had a history of smoking, 19.3% (29) had a history of tobacco chewing, and 12.66 (19) had other addictions (paan, ganja).

About 2.7% (4) were educated up to primary school 48% (72) have passed the middle school, 43.3% (65) high school, and only 6% (9) have a graduation degree. About 11.3% (17) were carpenters or involved in wood-related factories, 24% (36) were manual laborers, 9.3% (14) were farmers, 8.7% (13) were employed in government jobs, 36% (54) were working in private firms or running their businesses, and 10.7% (16) were either housewives or unemployed.

Among the patient, total duration of COPD ranged from 0.00 to 40 (years) and the mean duration was 5.38 ± 6.40 (years). The duration of inhaler ranged from 0.00 to 12 (years) and the mean duration for the study group was 2.12 ± 2.57 (years). About 82.7% (124) patients out of 150 were using an inhaler. The inhaler demonstration was seen in only 20% (30) of the participants and only 6.7% (10) participants have performed pulmonary function tests previously. The FEV_1 ranged from 36 to 70 and the mean FEV_1 of the study group was 51.9 ± 7.63. The FVC ranged from 052 to 102 and the mean FVC was 83.11 ± 10.2. The FEV_1/FVC ratio ranged from 50 to 69.5 and the mean ratio for the study group was 62.12 ± 6.86.

Cognitive Impairment and MOCA Scoring

Montreal cognitive assessment score was used to measure cognitive impairment in the study participants. Six different dimensions are used to measure cognitive function such as execution, naming, memory, attention, language, abstract, delayed recall, and orientation. The mean value obtained in each dimensions in this study is shown in Table 1. The different domains of MOCA with the frequency

of participants having different scores are given in the following Table 2. The total MOCA score was 30 and it ranged from 12 to 27 with an average score of 19.73 ± 2.55. The cutoff score was 26. 92.7% (139) patients had score <26 and 7.3% (11) had score ≥26 as shown in Table 3.

The study participants followed ten steps for using an inhaler. As shown in Table 4, step 1 was correctly done by all 100% (150) participants followed by step 2 and step 10 by 96.7% (145) participants and step 5 by 88.7% (133) participants, step 9 by 77.3% (116), and step 8 by 69.3% (104) participants. Step 6 was done correctly done by only 28% (42) participants. The mean value and range for different domains of MOCA are listed in the following Table 5. Among the different domains, language and abstract were the most commonly affected among those with MOCA score <26.

The study participants were divided into two groups, one with MOCA score <26 and the other with MOCA score ≥26. In participants with MOCA score<26, the average baseline inhaler score was 6.79 ± 0.75 and in participants with MOCA score ≥26 the baseline score 6.64 ± 1.0. $P = 0.521$ and it was not statistically significant. The mean total score at follow-up in participants with MOCA <26 was 6.00 ± 0.77 and in MOCA score ≥26 was 6.09 and was not statistically significant with $P = 0.19$ as shown in Table 6. In this study, as shown in Table 7, there was statistical significant association of MOCA with age with $P = 0.003$.

Table 1: The mean value in each domains of MOCA scoring

Domains	Mean (*n*=150)	Standard deviation	Range
Execution	2.91	0.61	0.00–4.00
Naming	1.94	0.59	0.00–3.00
Memory	2.19	0.75	0.00–4.00
Attention	2.42	0.85	0.00–4.00
Language	1.09	0.58	0.00–3.00
Abstract	1.18	0.64	0.00–3.00
Delayed recall	2.34	0.65	0.00–4.00
Orientation	5.67	0.55	3.00–6.00
Total score	19.73	2.55	12.00–27.00

DISCUSSION

Cognition is an ability that allows learning and correctly processing information from the environment for its subsequent retrieval and use. Cognitive impairment is defined as a moderate decline in function from baseline performance in one or more of six cognitive domains, where the deficits are insufficient to impair independent functioning. It can present as mild or severe form. It can present with memory loss, difficulty in judgment, recognizing the familiar persons and places, planning and carrying out tasks, frequent changes in mood and behavior. Risk factors for the development of mild cognitive impairment are age being the most important, hypertension, hyperlipidemia, coronary artery disease, stroke, family history of cognitive impairment, COPD, diabetes mellitus, depression, and other lifestyle factors.[11]

This study was conducted among COPD outpatients attending Medicine OPD of GTB hospital for a regular check-up and follow-up. The purpose of this study was to assess cognitive impairment in COPD patients (using MOCA) and to study the association of cognitive impairment with the understanding of inhaler technique. MOCA score was used for the screening of cognitive impairment which is a rapid screening test and can be easily administered on an OPD basis with minimal resources and has better sensitivity than other methods like MMSE.

In this study, out of 150 patients enrolled in the study, the mean age of the patients was 54.52 ± 5.99 years and 51.3% (77) of the participants were in the age group of 55–60 years. Males comprised 81.3% (122) and females comprised 18.7% (28). About 48% (72) had completed middle school, 43.3% (65) completed high school, and only 6% (9) have completed graduation. 102 (68%) had a history of smoking as the most common risk factor for the disease followed by tobacco chewing seen in 19.3%. The exposure to biomass fuel was seen in 74.7% (112), followed by industrial smoke in 19.3% (29), and air pollution in 3.3% (5). The mean FEV_1 was 51.99 ± 7.63, FVC being 83.11 ± 10.22, and the FEV_1/FVC ratio was 62.12 ± 6.86. The

Table 2: Distribution of the patients with respect to the scores in various domains of MOCA

Score	Execution		Naming		Memory		Attention		Language		Abstract		Delayed recall		orientation	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
0	1	0.7	2	1.3	2	1.3	2	1.3	17	11.3	11	7.3	1	0.7	0	0
1	1	0.7	25	16.7	20	10.7	16	10.7	105	70.0	109	72.7	7	4.7	0	0
2	26	17.3	103	68.7	79	52.7	63	42.0	26	17.3	22	14.7	87	58	0	0
3	105	70.0	20	13.3	45	30.0	55	36.7	2	1.3	8	5.3	50	33.3	1	0.7
4	17	11.3	-	-	4	2.7	14	9.3	-	-	-	-	5	3.3	3	2.0
5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	41	27.3
6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	105	70.0

mean duration of the disease was 5.38 ± 6.40 years and the average duration for use of inhaler was 2.12 ± 2.57 years. The mean total MOCA score was 19.73 ± 2.55 with a score ranging from 12 to 27.

Among the various domains of MOCA, it was observed that in this study, "language," "abstract," and "naming" were the most commonly affected among those with cognitive impairment (score<26) and there was statistically significant ($P < 0.001$) association.

The total score for correctly using the inhaler technique was 6.78 ± 0.77 at baseline and 6.01 ± 0.79 after a follow-up period of 15 days. The difference in the inhalation score at the follow-up was observed to be 1.08 ± 0.76. An error in at least one step of the inhalation technique was seen in 96.7% of participants. Cognitive impairment as defined in our study as MOCA scores <26 was observed in 92.7% (139) and a score of ≥26 was seen in 7.3% (11).

In a cross-sectional study by Dal Negro *et al.*, the extent and prevalence of cognitive dysfunction in COPD the study group comprised 402 participants out of which 229 were of COPD. The mean age for the study was 70 ± 12.9 years ranging from 40 to 79 years and males were 158 (68.9%) and females were 71 (31.0%) in number. About 82.1% were current or active smokers. The mean FEV_1 was 54.9 ± 23.6 and mean FEV_1/FVC ratio was 52.7 ± 11.9. They used MMSE, Clock drawing test, and Trail making test for assessing the cognitive impairment out of which trail making test and MMSE positively correlated with FEV_1 severity. Memory, attention, symbolic representation and visual processing, reproduction of numeric sequences, cognition flexibility, and shifting capacity were the most affected cognitive functions.[12] The mean FEV_1 was comparable to our study and they also observed cognitive impairment starting in the earlier stages of COPD.

Thakur *et al.* published in their study that the role of hypoxemia on cognitive impairment in COPD on 1202 participants. The mean age for the study was 58.2 ± 6.2 years (45–65 years) and females comprised 57.4% ($n = 691$). Current and ex-smokers were 87% ($n = 1027$). About 29% of the total participants have completed high school. MMSE was used as the screening tool for cognitive impairment and risk for cognitive impairment was seen with a positive odds ratio of 2.86 (1.34–7.46) and confidence interval of 95%.[13] Their study also observed a high prevalence of smoking as a risk factor similar to this study. The age of their study group was comparable to ours but they did also find an association between comorbidities and risk of cognitive impairment.

Turan *et al.* conducted a study to evaluate parameters affecting inhalation therapy adherence in elderly patients with COPD and asthma. Out of the total 121 participants recruited, 88 were of COPD. The mean age group was 70.24 ± 5.85 years. Females comprised 13.6% ($n = 12$) and males comprised 86.4% ($n = 76$). The male and female ratio of their study was similar to our study. A majority of their study group had completed only primary education (63.6%) and the average duration of their disease was 4.77 years which was very similar to 5.38 year seen in our study. The mean FEV_1 was 53.70 ± 16.85 and FEV_1/FVC ratio was 64.92 similar to seen in our study. They used MMSE as the tool for cognitive impairment and cognitive impairment was observed in 40.2%. The average inhaler device score was 7.01 ± 1.96.[14] The higher cognitive impairment observed in our study could be because of better sensitivity of MOCA to detect cognitive impairment.

Table 3: Distribution of patients according to total MOCA score

Score	Frequency (*n*=150)	Percentage (%)
<26	139	92.7
>26	11	7.3

Table 4: Distribution of participants according to correct inhaler technique for various steps of using the inhaler at baseline and at follow-up

Steps of inhaler technique	Frequency (*n*=150)	Percentage (%)	Frequency (follow-up)	Percentage (follow up)
Step 1 (remove cap)	150	100	144	96
Step 2 (hold the inhaler and shake it well)	145	96.7	75	50.0
Step 3 (breathe out gently)	69	46	107	71.3
Step 4 (put mouthpiece between teeth without biting)	133	88.7	126	84.0
Step 5 (start to breathe in slowly through the mouth and press down firmly on the canister)	56	37.3	59	39.3
Step 6 (continue to breathe in slowly and deeply)	42	28.0	38	25.3
Step 7 (hold breath for about 10 s)	57	38	39	26.0
Step 8 (while holding breath , remove the inhaler from the mouth)	104	69.3	73	48.7
Step 9 (breathe out gently away from the mouthpiece)	116	77.3	96	64.0
Step10 (replace cap)	145	96.7	144	96.0

Table 5: Comparisons of domains of MOCA scores

Domains	MOCA				*P*-value
	<26 (*n*=139)		>26 (*n*=11)		
	Mean	SD	Mean	SD	
Execution	2.84	0.57	3.73	0.47	<0.001
Naming	1.89	0.57	2.55	0.52	<0.001
Memory	2.13	0.71	3.00	0.77	<0.001
Attention	2.34	0.81	3.45	0.69	<0.001
Language	1.01	0.52	2.00	0.45	<0.001
Abstract	1.10	0.56	2.18	0.75	<0.001
Delayed recall	2.25	0.58	3.45	0.52	<0.001
Orientation	5.64	0.56	6.00	0.00	<0.037

Table 6: Difference in inhaler technique scores with respect to MOCA score

	MOCA				*P*-value
	<26 (*n*=139)		>26 (*n*=11)		
	Mean	SD	Mean	SD	
Baseline total score	6.79	0.75	6.64	1.03	0.521
Follow-up total score	6.00	0.77	6.09	1.04	0.715
Difference	1.06	0.76	1.36	0.67	0.197

Table 7: Distribution of participants with respect to MOCA status among different age groups

Age (years)	MOCA				*P*-value
	MOCA<26 (*n*=139)		MOCA>26 (*n*=11)		
	No.	Percentage	No	Percentage	
40–45	18	90	2	10	0.003
46–50	27	100	0	0	
51–55	23	88.5	3	11.5	
56–60	71	92.2	6	7.8	

A similar cross-sectional observation study was done by Mourad *et al.* to study cognitive profile in patients of COPD and asthma. Out of a total of 100 study participants, 40 were of COPD and the mean age was 60 ± 19.85 years, and males comprised 75% (n = 30) and females 25% (n = 10). The average duration of the disease was 13.2 ± 5.62 years. The mean FEV_1/FVC was 61.25 ± 17.51. They also used MOCA as the screening tool and the average MOCA score was 16.4 ± 6.30. The occurrence of cognitive impairment was observed in 85% of the COPD participants. They observed a significant association of age with cognitive impairment but did not found any association of gender, duration of disease, FEV1 with cognitive impairment.[15] This study had results similar to ours and observed a high occurrence of cognitive impairment.

In a cohort study done by Ersel Dag *et al.* in 2013, the study participants were in the age group of 43–79 years with a mean age of 64.9 ± 9.4 years and had 47 males and five females of the total 52 participants. The mean FEV_1 was 50.5 ± 17.5 in their study. For cognitive dysfunction, they used MOCA and MMSE and the proportion of subjects with COPD with cognitive impairment as measured by MOCA was 12% and they also found a significant association of age with cognitive impairment.[16] The huge difference in cognitive impairment from our study could be attributed to the difference in the sample size and literacy.

In a prospective cross-sectional study conducted by Hung *et al.* among 103 outpatients of COPD to evaluate the use of inhaler devices, 77 patients (74.8%) performed at least one essential step incorrectly for all devices. For the pMDI, the steps "breathe out gently to residual volume" and "shake inhaler thoroughly" were most frequently performed incorrectly.[17] In this study, at least one error was done by 96.7% which could be because of higher cognitive dysfunction observed. The step which was most incorrectly performed was "to continue to breathe in slowly and deeply" followed by "start to breathe in slowly through the mouth and press down firmly on the canister" and "holding the breath for about 10 s or as long as comfortable." These same errors were observed at follow-up also.

CONCLUSION

Prompt identification and management of cognitive impairment can have an effective bearing on the management and clinical outcome. Screening of cognitive dysfunction should be part of the routine diagnostic procedures in COPD patients to grade the overall impact of patients' respiratory conditions and to decide the most effective therapeutic actions and strategies.

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Original Article

Prevalence of Hyponatremia in Chronic Liver Disease Patients and Its Correlation with the Severity of the Disease

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Abstract

Background: Hyponatremia has been most common electrolyte abnormality found among the patients with advanced cirrhosis indicating a poor prognosis. The present study was conducted to estimate the prevalence of hyponatremia in chronic liver disease (CLD) patients and to assess the correlation of hyponatremia with the severity of the CLD.

Materials and Methods: This was a cross-sectional study conducted among CLD patients admitted in a tertiary care hospital. The sociodemographic data, clinical history, and details about the risk factors of CLD were collected using a semi-structured questionnaire by interview method. Blood investigations were performed along with upper GI endoscopy. Severity of cirrhosis was assessed according to Child-Pugh score. Data were analyzed using SPSS version 18.0. $P < 0.05$ was considered statistically significant.

Results: The mean age of the study subjects was 45.19 ± 10.01 years and 92.0% were male. The prevalence of hyponatremia was 75.0% at the cut off of ≤135 mEq/L and it was 52.0% at the cut off of ≤130 mEq/L. Higher proportions of those with moderately impaired hepatic function and advanced hepatic dysfunction (Class B/Class C) had hyponatremia compared to those without hyponatremia (76.6% vs. 50.0%), but it was not statistically significant ($P > 0.05$). Significantly higher proportions of those with hyponatremia had hepatic encephalopathy (85.4%) compared to those with no hyponatremia (67.8%) ($P < 0.05$).

Conclusion: The prevalence of hyponatremia was noted to be 75.0%, but the severity as per Child-Pugh score had no association with hyponatremia. However, hepatic encephalopathy was significantly associated with hyponatremia.

Keywords: Child-Pugh score, Chronic liver disease, *Hyponatremia*

INTRODUCTION

Chronic liver disease (CLD) is a progressive disease of the liver with deterioration of liver functions for more than 6 months. Such liver functions include detoxification of harmful products of metabolism, excretion of bile and the synthesis of clotting factors, and other proteins. It is a continuous process of inflammation, destruction, and regeneration of liver parenchyma, leading to fibrosis and cirrhosis. The final stage of CLD, the cirrhosis, results in disruption of liver architecture, the formation of widespread nodules, vascular reorganization, neo-angiogenesis, and deposition of an extracellular matrix.[1]

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Cirrhosis is ranked as 11th leading cause of death and 15th leading cause of morbidity. It contributes for 2.2% of deaths and 1.5% of disability-adjusted life years worldwide as in 2016. 1.32 million deaths in 2017, nearly two-thirds among men and one-third among women are due to CLD.[2] According to the latest WHO data published in 2018, liver disease deaths, in India, are recorded as 3.0% of total deaths corresponding to 264,193 deaths. The age adjusted death rate being 23.0 per 100,000 population, it ranks India at 62nd position in the world.[3]

There is a wide-ranging spectrum of etiologies for CLD such as toxins, chronic alcohol abuse, infection with Hepatitis B and C, autoimmune diseases, and genetic and

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metabolic disorders.[1] Alcohol has been the most common etiology of cirrhosis, while hepatitis B virus was most common in the non-cirrhotic CLD and Hepatocellular carcinoma.[4] The signs and symptoms are nonspecific, which are anorexia, fatigue, and weight loss, or it depends on the complication that the patient would have developed. The three important complications of CLD are portal hypertension (esophageal varices and ascites), hepatocellular insufficiency (e.g., jaundice and hepatic encephalopathy), and hepatocellular carcinoma.[1]

Hyponatremia is decreased serum sodium below 130 mmol/L and is a common finding in patients with decompensated cirrhosis due to an abnormal regulation of body fluid homeostasis. It can be either be due to hypovolemia due to loss of extracellular fluid as a result of use of diuretics or due to expanded extracellular fluid volume due to the inability of the kidneys to excrete solute-free water proportionate to the amount of free water ingested.[5] A number of recent studies have shown the association of hyponatremia with greater severity of complications of cirrhosis, namely, difficult-to-control ascites, and greater frequency of complications post-transplant including neurologic disorders, renal failure, and infectious complications.[6] Hyponatremia is also found to be associated with increased morbidity and mortality in patients with cirrhosis.[5] As there were no studies on the effect of hyponatremia in CLD in the present study setting, this study was conducted to estimate the prevalence of hyponatremia in CLD patients and to assess the correlation of hyponatremia with the severity of the CLD in the present study setting.

MATERIALS AND METHODS

This was a cross-sectional study conducted for 18 months from November 2019 to May 2021 among CLD patients admitted in wards of the Department of Medicine of a tertiary care hospital situated in Bangalore after obtaining ethical clearance from the Institutional Ethics committee. From the previous study, considering prevalence of hyponatremia in liver cirrhosis as 52%,[7] estimated sample size was 99 ≈ 100 with 5% alpha error, 5% absolute precision, and considering 5% non-compliance using the formula $n = z^2(pq/L^2)$. After obtaining written informed consent, 100 patients with CLD admitted in the hospital were included in the study by purposive sampling. The sociodemographic data, clinical history, and details about the risk factors of CLD were collected using a semi-structured questionnaire by interview method. Clinical history included age, sex, and history of alcohol intake. Clinical examination included vitals, general examination, and systemic examination which were done. Venous blood samples were drawn at the time of admission before initiation of treatment. All blood samples were processed within 30 min of blood collection using an autoanalyzer. Investigations included complete hemogram, serum electrolytes, serum urea and creatinine, liver function test, serum albumin, and prothrombin time. Upper GI endoscopy was performed on all the patients. Severity of cirrhosis was assessed according to Child-Pugh score.

The Child-Pugh scoring system[8] (also known as the Child-Pugh-Turcotte score) was designed to predict mortality in cirrhosis patients. The original scoring system conceptualized by Child and Turcotte in 1964 used five clinical and laboratory criteria to categorize patients: serum bilirubin, serum albumin, ascites, neurological disorder, and clinical nutrition status. The scoring system was modified later by Pugh *et al.*, substituting prothrombin time for clinical nutrition status. In addition, they introduced variable points for each criterion based on increasing severity:

- Encephalopathy: None = 1 point, Grades 1 and 2 = 2 points, and Grades 3 and 4 = 3 points
- Ascites: None = 1 point, slight = 2 points, and moderate = 3 points
- Bilirubin: under 2 mg/ml =1 point, 2–3 mg/ml =2 points, and over 3 mg/ml =3 points
- Albumin: >3.5 mg/ml =1 point, 2.8–3.5 mg/ml =2 points, and <2.8 mg/ml =3 points
- Prothrombin Time* (sec prolonged): <4 s = 1 point, 4–6 s = 2 points, and over 6 s = 3 points.

*Frequently, INR will be used as a substitute for PT, with INR under 1.7 = 1 point, INR 1.7–2.2 = 2 points, and INR above 2.2 = 3 points.

The severity of cirrhosis classified as:

- Child-Pugh A: Good hepatic function – 5–6 points
- Child-Pugh B: Moderately impaired hepatic function – 7–9 points
- Child-Pugh C: Advanced hepatic dysfunction – 10–15 points.

Operational definition

Hyponatremia was considered at the serum sodium levels of cut off of ≤135 mEq/L.

Statistical analysis

Data were entered in excel and the categorical data were presented as proportions and the continuous data were presented in mean ± SD. The categorical variables were analyzed using Chi-square test and Fisher's exact test. The means were compared among the groups of Child-Pugh class using one-way ANOVA. SPSS Statistics version 18.0 (IBM Corp., USA). $P < 0.05$ was considered statistically significant.

RESULTS

Majority of the study subjects, that is, 39.0% were in the age group of 46–55 years and almost all (92.0%) were male. The mean age of the study subjects was 45.19 ± 10.01 years and the age ranged from 25 years to 73 years. The most common etiology of CLD being alcohol (94.0%) were chronic alcohol drinkers for more than 10 years (72.9%) and nearly more than half, that is, 63.5% were consuming an alcohol of more than 60 g per day [Table 1].

The average levels of total protein and albumin levels in g/day were 5.7 and 2.2, respectively. The median total bilirubin and direct bilirubin levels were 4.95 mg/dL and 3.00 mg/dL, respectively. The median serum glutamic oxaloacetic transaminase levels were 92.0 U/L, serum glutamic pyruvic transaminase was 44.5 U/L, and alkaline phosphatase was 124 U/L [Table 2].

Most of them (90.0%) had ascites, 56.0% had splenomegaly, 41.0% had hepatic encephalopathy of varied severity, and higher proportions of study subjects had developed portal hypertension (93.0%). Majority of the study subjects (77.0%) had advanced hepatic dysfunction according to Child-Pugh classification [Table 3].

The prevalence of hyponatremia was noted to be 75.0% considering the cut off of ≤135 mEq/L and it was 52.0%, when the cut off of ≤130 mEq/L was considered. However, 78.7% of those with hyponatremia had advanced hepatic dysfunction as per Child-Pugh Score. The mean sodium levels was 130.93 ± 6.12 mEq/L and the minimum and maximum levels of sodium among the study subjects were 113 mEq/L to 146 mEq/L [Table 4].

Among various sociodemographic such as age, gender, and alcohol intake and complications of CLD such as ascites, hepatic encephalopathy, and portal hypertension, significantly higher proportions of those with hyponatremia had hepatic encephalopathy (85.4%) compared to those with no hyponatremia (67.8%) ($P < 0.05$).

Higher proportions of those with moderately impaired hepatic function and advanced hepatic dysfunction (Class B/Class C) had hyponatremia compared to those without hyponatremia (76.6% vs. 50.0%), but it was not statistically significant ($P > 0.05$).[Table 5]

Table 1: Sociodemographic and clinical details of the study subjects (*n*=100)

Variables	Frequency, *n* (%)
Age-group (years)	
≤35	21 (21.0)
36–45	27 (27.0)
46–55	39 (39.0)
>55	13 (13.0)
Gender	
Males	92 (92.0)
Females	8 (8.0)
Etiology of chronic liver disease	
Alcohol	94 (94.0)
Infective (Hep B)	2 (2.0)
Both	4 (4.0)
Alcoholic (g/day) (*n*=96)*	
≤60	35 (36.5)
61–120	46 (47.9)
121–180	15 (15.6)
Duration of alcoholism (years) (*n*=96)*	
≤10	26 (27.1)
11–20	58 (60.4)
>20	12 (12.5)

*04 are non-alcoholics

Table 2: Average levels of different blood parameters (*n*=100)

Blood parameters	Median (range)
Total protein (g/dL)	5.70 (3.50–8.00)
Total albumin (g/dL)	2.20 (1.10–4.80)
Total bilirubin (mg/dL)	4.95 (0.50–34.40)
Direct bilirubin (mg/dL)	3.00 (0.1–25.10)
SGOT (U/L)	92.0 (15–1405)
SGPT (U/L)	44.5 (10–1642)
Alkaline phosphatase (U/L)	124.0 (13.0–430.0)

SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase

Table 3: Signs of chronic liver disease and severity of liver disease according to Child-Pugh class (*n*=100)

Variables	Frequency, *n* (%)
Ascites	
Yes	90 (90.0)
No	10 (10.0)
Splenomegaly	
Yes	56 (56.0)
No	44 (44.0)
Hepatic encephalopathy	
0	59 (59.0)
1	6 (6.0)
2	15 (15.0)
3	9 (9.0)
4	11 (11.0)
Portal hypertension	
Yes	93 (93.0)
No	7 (7.0)
Child-Pugh class	
A	6 (6.0)
B	17 (17.0)
C	77 (77.0)

Table 4: Prevalence of hyponatremia

Hyponatremia	Child-Pugh class			Total
	Class A	Class B	Class C	
Yes	3 (4.0)	13 (17.3)	59 (78.7)	75 (75.0)
No	3 (12.0)	4 (16.0)	18 (72.0)	25 (25.0)

Table 5: Association of hyponatremia with sociodemographic, complications, and severity of chronic liver disease (*n*=100)

Variables	Hyponatremia		χ^2 (*P*)
	Yes	No	
Age-group (years)			
≤45	38 (79.2)	10 (20.8)	0.86 (0.36)
>45	37 (71.2)	15 (28.8)	
Gender¥			
Males	68 (74.7)	23 (25.3)	(1.00)
Females	7 (77.8)	2 (22.2)	
Alcohol intake¥			
Yes	71 (74.0)	25 (26.0)	(0.57)
No	4 (100.0)	0 (0.0)	
Ascites			
Yes	67 (74.4)	23 (25.6)	(1.00)
No	8 (80.0)	2 (20.0)	
Hepatic encephalopathy			
Yes	35 (85.4)	06 (14.6)	3.98 (0.04)*
No	40 (67.8)	19 (32.3)	
Portal hypertension			
Yes	70 (75.3)	23 (24.7)	(1.00)
No	5 (71.4)	2 (28.6)	
Child-Pugh class			
Class A	3 (50.0)	3 (50.0)	(0.16)
Class B/C	72 (76.6)	22 (23.4)	

*Indicates statistically significant association, ¥Fisher's exact test applied

The mean levels of sodium were lesser in Class B (130.53 mEq/L) and Class C (130.82 mEq/L) severity of CLD compared to Class A (133.50 mEq/L) as per Child-Pugh score ($P > 0.05$).

DISCUSSION

CLD is a condition with deranged hepatic functions and hyponatremia is noted to be common in about half of the hospitalized patients.[9,10] Understanding the prevalence of hyponatremia and its association with the CLD in the present study, setting would help in the better management of advanced liver disease. Hence, the present study was conducted.

Malani *et al.* have reported a mean age of 58 years and majority were male with most common etiology of CLD being alcohol which are almost in line with the present study findings, but for the mean age which was lesser in ours (45 years) and also the proportions which were more in our study setting. The differences in the distribution of patients might be due to the different study settings.[9] However, the distribution of the patients with respect to age and gender and also the etiology of CLD according to Nareddy *et al.* was same as our study findings.[10] Nearly 3/4th (72.9%) of our study subjects were chronic alcoholics for more than 10 years and nearly more than half, that is, 63.5% were consuming an alcohol of more than 60 g per day.

Kumar and Ashok had found ascites among all the patients and hepatic encephalopathy among 18% of them, whereas 90.0% of our study subjects had ascites and 41.0% of them had hepatic encephalopathy.[11] Portal hypertension was reported among 93.0% of our subjects and it is postulated that splenomegaly can manifest following portal hypertension and it also contributes to the progression to cirrhosis, where 56.0% of our subjects had splenomegaly in the current study.[12] Dhanorkar and Galande found hepatic encephalopathy Grades I, II, III, and IV among 24.0%, 27.0%, 30.0%, and 39.0% in patients with liver cirrhosis, respectively, and 6.0%, 15.0%, 9.0%, and 11.0% in ours had, respective hepatic encephalopathy of Grades I, II, III, and IV which were relatively lesser in our subjects indicating relatively lesser complications compared to theirs.[13]

Majority of the study subjects (77.0%) had advanced hepatic dysfunction according to Child-Pugh classification in our study. Similarly, Nareddy *et al.* have reported that majority of their patients (72.6%) belonged to Child-Pugh C (72.6%).[10]

About 49.4% of those with liver cirrhosis had hyponatremia as per Singh *et al.*[14] and it was 53.0% as per Reddy *et al.*[15] The prevalence of hyponatremia was noted to be 75.0% which was higher among our study subjects and is dependent on other factors such as release of arginine vasopressin, production of solute-free water, and resorption of sodium in proximal tubule and is also said to be associated with many complications such as severe ascites and hepatic encephalopathy.[6] Nareddy *et al.* found 34.7% to have hyponatremia when the cut-off of ≤ 130 mEq/L was considered and 52.0% were affected in ours and as said earlier, it is dependent on other factors.[6,10] Based on the findings of Malani *et al.*, 20.0%, 23.8%, and 91.7% of the patients belonging to Child-Pugh Scores A, B, and C, respectively, had with hyponatremia; however, in ours, the proportions were higher and it was 50.0%, 76.5%, and 76.6% except for Class C which was higher in theirs.[9]

In our study, the overall mean sodium levels were 130.93 ± 6.12 mEq/L and the levels were lesser in Class B (130.53 mEq/L) and Class C (130.82 mEq/L) compared to Class A (133.50 mEq/L) as per Child-Pugh scores. Similarly Raja *et al.* recorded mean sodium levels of 133.5 meq/L in Class B patients and Class C patients sodium levels were 124.8 meq/L based on Child-Pugh scores and the difference was found to be statistically significant; however, the significance could not be established in ours as the levels were nearly same in Class B and C which depends on the severity of the liver disease.[7] Higher proportions of those with moderately impaired hepatic function and advanced hepatic dysfunction (Class B/Class C) had hyponatremia compared to those without hyponatremia

(76.6% vs. 50.0%), but it was not statistically significant. However, Nareddy *et al*. have found the significant association of hyponatremia with advanced liver disease as per Child-Pugh Class C [10]. Hyponatremia were associated with increased frequency of hepatic encephalopathy according to Gupta *et al*. and Gadhwal and Arif; similarly, in ours, it was significantly associated.[16,17] Younus A *et al*. also have established similar association.[18] Hyponatremia is known to affect the brain function and hence is said to predispose hepatic encephalopathy [14].

Further in-depth study in a larger setting may help us to get a deeper insight in eliciting the causal relationship between severity of liver disease and hyponatremia.

CONCLUSION

The prevalence of hyponatremia was seen in 3/4th (75.0%) of those with CLD in our study. However, the proportions of those with hyponatremia increased with severity of CLD, but for the significance, the levels of sodium did not differ much with severity of liver diseases as per the Child-Pugh classification. However, our study highlights a significant association of an important complication of hepatic encephalopathy with hyponatremia. Hence, serum sodium levels might indicate the complication in CLD.

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Original Article

A Study on the Morphometric Profile of Glenoid Part of Human Scapula

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Abstract

Introduction: Shoulder instability is a challenging part for an orthopedic surgeon to diagnose and treat due to various anatomical and pathological changes which occur in the glenoid cavity of scapula. In shoulder arthroplasty, the prosthesis of glenoid component of scapula is used to treat conditions such as complete glenoid erosion and severe glenoid fracture. Therefore, we aimed to establish the morphometric and morphological features of glenoid cavity of scapulae harvested from a sample of population of Tamil Nadu.

Aims and Objectives: The aim of the study is to establish the morphometric profile of glenoid part of human scapula present in the Department of Anatomy, Government Medical College, Pudukkottai.

Materials and Methods: We studied 65 dry scapulae (30 right, and 35 left) from the Department of Anatomy, Government Medical College, Pudukkottai, Tamil Nadu. Vertical diameter of the glenoid cavity, transverse diameter of the lower half, and upper half of the glenoid cavity were measured. The shape of the glenoid cavity and the incidence of distinct glenoid notch were also noted.

Results: The mean vertical diameter of glenoid cavity was 3.63 ± 0.3 cm on the right and 3.58 ± 0.3 cm on left side. The mean transverse diameter of lower half of glenoid cavity was 2.52 ± 0.3 cm on the right and 2.50 ± 0.3cm on the left side. The mean transverse diameter of the upper half of glenoid cavity was 1.93 ± 0.2 cm on the right and 1.91 ± 0.3 cm on the left side. Pear-shaped glenoid cavity was noted in 56% of scapula, oval shape was seen in 29%, while inverted comma shape was observed in 15% of scapula.

Conclusion: Knowledge of morphometry and morphology of glenoid cavity of scapula helps design the glenoid component of scapula for arthroplastic procedure. Knowledge of variation in normal anatomy of glenoid fossa is necessary to diagnose and treat the conditions such as glenoid erosion, Bankart lesion, and osteochondral defects.

Key words: Bankart lesion, Glenoid cavity, Glenoid notch, Shoulder instability

INTRODUCTION

The scapula is a flat triangular bone present on the posterolateral aspect of the thorax. The glenoid cavity is a fossa present in the lateral part of the scapula, which provides a shallow socket for the head of the humerus to articulate.[1] Such a shallow fossa makes the shoulder joint, the most frequently dislocating joint in the body. Depending on the presence of a glenoid notch in its anterior margin, the shape of the glenoid cavity takes an inverted comma shape or a pear shape or an oval shape.[2]

In anterior shoulder dislocation, patients with distinct glenoid notch are more prone for anterior glenoidlabral tear (Bankart lesion), due to the non-attachment of labrum in the notch.[3] Hence, the present study noted the incidence of distinct glenoid notch and the various shapes of glenoid cavity in the Tamil Nadu population. Glenoid erosion is considered to be one of the most important causes for recurrent shoulder instability.[4] To diagnose the percentage of erosion, the normal morphometric parameters of the glenoid cavity are needed.

Fracture of glenoid is also quite common in acute trauma of the shoulder joint.[5] To manage it, the prosthesis of glenoid component of the scapula is needed.[6] In the

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view of above consideration, we aimed to establish the morphometric and morphological parameters of glenoid cavity of the scapula in Tamil Nadu population.

Aims and objectives

The aim of the study is to establish the morphometric profile of glenoid part of human scapula present in the Department of Anatomy, Government Medical College, Pudukkottai.

MATERIALS AND METHODS

The study was done on 65 dry unpaired scapulae (30 right, and 35 left) of unknown sex from the Department of Anatomy, Government Medical College, Pudukkottai, Tamil Nadu. Damaged bones were excluded from this study. The following parameters were measured.

As shown in Figure 1, the vertical diameter of the glenoid cavity was measured by taking the maximum distance from the supraglenoid tubercle to the inferior margin of the glenoid cavity, the transverse diameter of the lower half of the glenoid cavity was measured by taking the maximum distance between the anterior margin and the posterior margin of the glenoid cavity and transverse diameter of the upper half of the glenoid cavity was measured by taking the anteroposterior diameter of the upper half of the glenoid cavity at the midpoint between the superior margin and the midpoint of vertical length of the glenoid cavity of the scapula. All the above parameters were measured with the digital caliper. The bones were examined for the various shapes of the glenoid cavity, as shown in Figure 2. The incidence of distinct glenoid notch, as shown in Figure 3, was also noted in our study. Statistical analyses such as mean, standard deviation, and the range were calculated using IBM SPSS statistical software (version 22.0) - IBM, New York, USA.

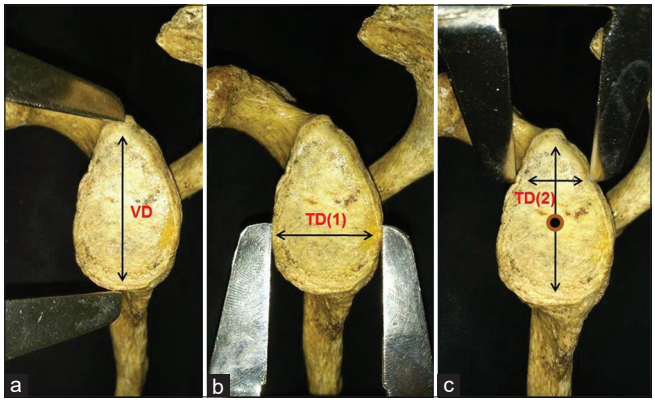

Figure 1: Diameters of glenoid cavity of scapula (a) vertical diameter of the glenoid cavity (VD), (b) transverse diameter of the lower half of the glenoid cavity (TD 1), and (c) transverse diameter of upper half of the glenoid cavity (TD 2)

RESULTS

As given in Table 1, the mean vertical diameter of the glenoid cavity on the right side was 3.63 ± 0.3 cm and it was 3.58 ± 0.3 cm on the left side. The mean transverse diameter of the lower half of the glenoid cavity on the right side was 2.52 ± 0.3 cm and it was 2.50 ± 0.3 cm on the left side. The mean transverse diameter of the upper half of the glenoid cavity on the right side was 1.93 ± 0.2 cm and it was1.91 ± 0.3 cm on the left side. As given in Table 2, out of 65 glenoid cavities examined, pear-shaped glenoid cavities were noted in 56%, oval shape was seen in 29%, and inverted comma shape in 15% of the bones. Distinct glenoid notch was noted in 17% of the scapula studied, as shown in Table 3.

DISCUSSION

The various anatomical and pathological changes in the glenoid cavity of the scapula make it more prone for shoulder instability and recurrent dislocation of the

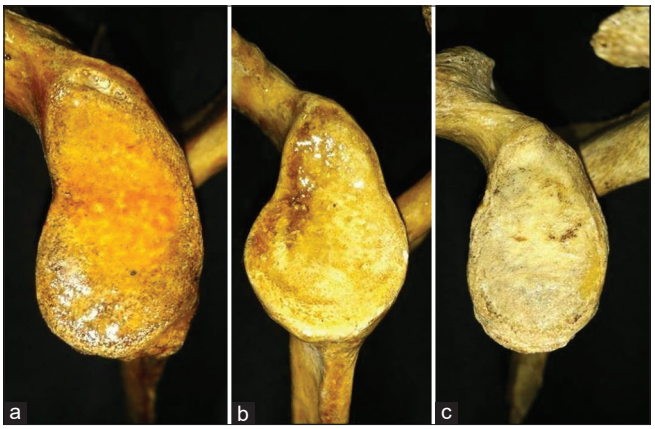

Figure 2: Shapes of glenoid cavity of scapula (a) inverted comma shape, (b) pear shape, and (c) oval shape

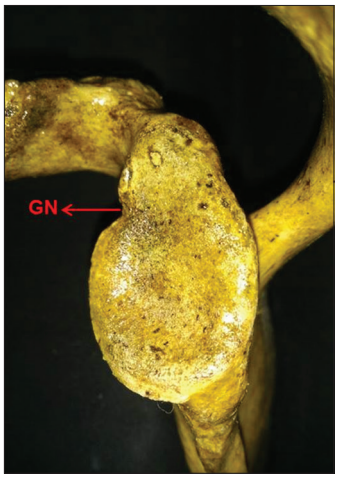

Figure 3: Distinct glenoid notch (GN) of scapula

Table 1: Morphometric parameters of the right and left glenoid cavities of scapula

Parameters (cm)	Mean±SD		Range	
	Right	Left	Right	Left
Vertical diameter	3.63±0.3	3.58±0.3	3–4.2	3–4.1
Transverse diameter (1)	2.52±0.3	2.50±0.3	2–3.3	2–3.2
Transverse diameter (2)	1.93±0.2	1.91±0.3	1.5–2.4	1.3–2.4

SD: Standard deviation

Table 2: Incidence of various shapes of glenoid cavity of scapula

Shape of the glenoid	Right side (%)	Left side (%)	Overall occurrence (%)
Inverted comma	20	14	15
Pear	53	54	56
Oval	27	32	29

Table 3: Incidence of distinct glenoid notch in scapula

Feature	Right side	Left side	Percentage
Distinct glenoid notch	7/65	4/65	17

shoulder joint. Among this, glenoid erosion is considered to be the major cause for shoulder instability due to its high risk of recurrence even after surgical repair. Hence, early diagnosis and the treatment of glenoid erosion are needed, which depends on the percentage of bone eroded versus normal joint surface area of the glenoid cavity, the width and the height of the glenoid cavity.[7]

According to Mamatha *et al.*[8] the mean vertical diameter of the glenoid cavity on the right side was 3.36 cm and it was 3.40 cm on the left side, the mean transverse diameter of the lower half of the glenoid cavity on the right side was 2.33 cm and it was 2.30 cm on the left side, and the mean transverse diameter of the upper half of the glenoid cavity on the right side was 1.62 cm and it was 1.57 cm on the left side. All these morphometric parameters were similar to our study values, as shown in Table 1. Our study results were similar to previous studies done by Rajput, Kavita and Jaskaran and Maman *et al.*[9-11]

Prescher and Klümpen,[2] in 1996, noted that the percentage of the glenoid cavity with both distinct and indistinct glenoid notch (inverted comma and pear shape) was 55%. However, in our study, it was found to be present in 69% of the bones studied.

As shown in Figure 3, the glenoid notch is a small depression present in the anterior rim of the glenoid cavity which alters the shape of the glenoid cavity as inverted comma, pear shape, and oval shape. The exact reason for the presence of the glenoid notch was not known. It could be suggested that the pressure on the anterior margin of the glenoid cavity by the tendon of subscapularis muscle leads to the formation of the notch. Frazer,[12] in 1958, suggested that the scapular part and the coracoid part of the glenoid cavity were marked by the glenoid notch. Prescher and Klümpen [13] suggested that the glenoid labrum was not attached to the margin of the glenoid cavity at the glenoid notch, but bridged it.

Bankart,[14,15] in 1923, and Adams, in 1948,[16] observed that labral tears and avulsion of the labrum occur at the anterior margin of the glenoid cavity (Bankart lesion) in a patient with recurrent dislocation. The nonattachment of the labrum in the glenoid notch could make the shoulder joint less resistant to dislocating forces and was found to be the predisposing factor for Bankart lesions. This lesion is an important cause for recurrent shoulder instability. In the present study, the incidence of glenoid notch in both right and left scapulae was 70%. Out of this, distinct glenoid notch was noted only in 17% of the bone studied. Hence, the normal non-attachment of the glenoid labrum at the glenoid notch must not be diagnosed as a Bankart lesion.

CONCLUSION

The morphometric and morphological parameters of the glenoid cavity observed in the present study will help the orthopedic surgeons to decide the proper size of the glenoid component of the scapula in shoulder arthroplasty. In shoulder instability cases, these morphometric parameters are helpful for the radiologist to diagnose and categorize the degree of glenoid erosion which helps in better surgical planning of the glenoid repair to prevent recurrent instability. The knowledge of various shapes of glenoid cavity and the incidence of glenoid notch noted in the present study are important for evaluating the pathological conditions such as osseous Bankart lesion and glenoid erosion in the shoulder instability.

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Original Article

Prevalence of Eye with Spectrum of Angle Closure in a Population Attending the Outpatient Department of a Tertiary Eye Care Center in Kolkata

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Abstract

Objective: The objective of this study was to determine the prevalence of eye with angle closure disease in a population attending the outpatient department of a tertiary eye care center in Kolkata.

Materials and Methods: The study was hospital-based cross-sectional study. Total of 150 patients visiting the outpatient department of a tertiary care eye center in Kolkata and satisfying the inclusion criteria were randomly selected. The patients were divided into groups according to their age, and each group underwent complete ocular examination. The total study was for 16 months (January 1, 2019–April 30, 2020). Subjects underwent detailed ophthalmic examination including slit lamp examination, intraocular pressure measurement, gonioscopy, streoscopic fundus examination, automated visual field testing, and Heidelberg Spectralis Oct fast retinal nerve fiber layer scan.

Results: Results were analyzed using Chi-square test and multiple logistic regressions using SPSS 25(IBM). Mean age was 46.1 ± 6.05 years. The prevalence was more in females (65%) than males (35%). Out of which,78 patients had primary angle closure suspect (PACS) (52%; CI 95%, 44.1–59.8%), 52 patients had primary angle closure (PAC) (34.6%; CI 95%, 27.5–42.5%), and 20 patients had PAC glaucoma (PACG) (13.3%;CI 95%, 8.8–19.6%). One hundred and twelve were chronic (74.6%), while 38 patients were acute (25.3%) patients of PAC disease (PACD). Ninety-two patients were asymptomatic (61.3%) and 58 were symptomatic (36.6%) on presentation.

Conclusion: As per this study, it was concluded that higher age and females were most affected. PACS was the most common subtype. Most of the patients were found to be chronic asymptomatic.

Key words: Prevalence, Primary angle closure disease, Primary angle closure glaucoma, Primary angle closure suspect, Primary angle closure

INTRODUCTION

Acute angle closure glaucoma is an ocular emergency and receives distinction due to its acute variation, need for immediate treatment, and well-established anatomic pathology.[1] Rapid diagnosis and immediate intervention and referral can have profound effect on a patient's outcome and morbidity. There is a wide variation in the prevalence of the primary angle closure glaucoma (PACG) within India.

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Angle closure disease is the leading cause of irreversible blindness and is an important Public Health issue. Population-based studies are important for assessment of disease burden, health care policy planning, and appropriate resource allocation. Asians represent 47% of those with glaucoma[2] and 7% of those with angle closure disease. The prevalence of PACG in southern India ranges from 0.5% to 4.30%,[3] where as in Eastern India, it was only 0.23%.[4]

The aim of this study was to determine the prevalence of eye with spectrum of angle closure in a population

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attending the outpatient department of a tertiary eye care center in Kolkata.

MATERIALS AND METHODS

Population-based studies are important for assessment of disease burden, health care policy planning, and appropriate resource allocation. This is a hospital-based cross-sectional study which was conducted in patients visiting the outpatient department of a tertiary eye care center in Kolkata. One hundred and fifty patients attending the outpatient department were randomly selected. The study commenced on January 2019 and concluded on June 2020. The Institutional Ethics Review Board approved the study that adhered to the tenets of the Declaration of Helsinki.[5]

The patients who came to the outpatient department were randomly selected and were divided into groups according to their age, and each group underwent complete ocular examination. On arrival at the examination center, the subjects were requested to sign an informed consent. In the case of illiterate subjects, the consent form was read out to them in their vernacular language in the presence of either a relative or a community volunteer. The left thumb impression was used as a signature for illiterate patients.

They then proceeded through various ophthalmic examinations and diagnostic procedures in the following order:[6,7]

a. Ocular and medical history
b. Lensometry was performed where necessary
c. Refraction and recording of best-corrected visual acuity
d. Pupillary evaluation
e. Corneal pachymetry: The central corneal thickness was measured using the ultrasound pachymeter
f. Slit lamp bio-microscopy, including van Herrick grading of the angle of the anterior chamber angle, was performed
g. Applanation tonometry: Intraocular pressure (IOP) recording with the Goldmann applanation tonometer was done. Calibration was done by trained senior glaucoma surgeons on a weekly basis
h. Gonioscopy: A Goldmann's 3-mirror hand-held gonioscope was used, and the angle was graded according to the Shaffer system. Gonioscopy was performed in dim ambient illumination with a shortened slit that did not fall on the pupil. An angle was considered occludable if the pigmented trabecular meshwork was not visible in >270° of the angle in dim illumination. All subjects with occludable angles in one or both the eyes were deemed to have primary angle closure disease (PACD). If the angle was occludable, indentation gonioscopy was performed, and the presence or absence of peripheral anterior synechia was recorded. Laser iridotomy was performed in subjects with occludable angles after obtaining their consent. The rest of the examination was deferred to another convenient date following laser iridotomy.
i. Grading of lens opacities (Lens Opacities Classification System II)
j. Fundus examination using +90 D lens
k. Optic disk evaluation was done using + 78D lens. The vertical cup-disk ratio was recorded, and a special note was made of peripapillary atrophy and optic disc/peripapillary hemorrhage, bayoneting sign, baring of circumlinear vessels, and laminar dot sign
l. Automated visual field testing was done in all subjects using Humphrey field analyzer using central 24-2 SITA standard test
m. Heidelberg spectralis Oct fast retinal nerve fiber layer (RNFL) scan was employed to determine RNFL analysis.

The following definitions based on INTERNATIONAL SOCIETY GEOGRAPHICAL AND EPIDEMIOLOGICAL OPHTHALMOLOGY guidelines[8-10] were used for the current work.

Primary Angle Closure Suspect (PACS)

Gonioscopy shows posterior meshwork iridotrabecular contact (ITC) in three or more quadrants but no Peripheral Anterior synechiae (pas). Many patients with less ITC have evidence of intermittent angle closure, and a lower threshold for diagnosis, such as, two quadrants of ITC, pigment smudging or even a very narrow angle approach, 20° or less, maybe justified.

1. Normal IOP, optic disk, and visual field
2. No peripheral anterior synechiae
3. The risk of PACG at 5 years maybe around 30%.

Primary Angle Closure (PAC)

1. Gonioscopy shows three or more quadrants of ITC with raised IOP and/or PAS, or excessive pigment smudging on trabecular mesh work
2. Normal optic disk and visual field.

PACG

1. ITC in three or more quadrants, with glaucomatous optic neuropathy
2. Optic nerve damage from an episode of severe IOP elevation, such as acute angle closure, may not appear as typical glaucomatous cupping.

Inclusion Criteria

The following criteria were included in this study:

1. Adult age group of more than 18 years and <55 years
2. Patients with PACD or PACS or PAC or PACG

3. Patients with acute or chronic onset of symptoms
4. Patients having either symptomatic or asymptomatic presentation.

Exclusion Criteria

Patients with secondary glaucomas and open angle glaucoma were excluded from the study.

Statistical Analysis

Data were collected on a standardized pro forma from all the subjects who were willing to participate in the study after taking informed written consent. Data were entered in Microsoft Excel sheet and analyzed by SPSS 25 IBM version. Quantitative data were expressed in mean ± S.D or median ± interquartile range. Qualitative data were expressed in proportions and percentages and associations, were calculated using Chi-square or Fischer exact test. $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 150 patients were enumerated who visited the outpatient department from January 2019 to June 2020. Data from all the 150 subjects were analyzed. Table 1 shows that the average age was 46.1 ± 6.05. 0.6% was in age 18–25 years, 4.6% were in 26–35 years, 36% were in 36–45 years, and 58.6% were in 46–55 years. The prevalence of glaucoma was found to be increasing in higher age groups. Out of 150 patients, 65% were female and 35% were male [Figure 1]. Hence, females are affected more as compared to males. In our study, 78 patients had PACS (52%; CI 95%, 44.1–59.8%), 52 patients had PAC (34.6% CI 95%, 27.5–42.5%), and 20 patients had PACG (13.3% CI 95%, 8.8–19.6%). Hence, higher prevalence was for PACS, while least prevalence was for PACG. Our study, Table 2 shows that higher age group has higher prevalence of PACS followed by PAC and PACG [Table 2].

One hundred and twelve were chronic (74.6%), while 38 patients were acute (25.3%) patients of PACD. Ninety-two patients were asymptomatic (61.3%) and 58 were symptomatic (36.6%) on presentation.

Table 1: Mean age with standard error and standard deviation among the study subjects

Mean	46.17
SEM	0.495
Median	47.00
SD	6.057
Variance	36.690
Range	31
Minimum	24
Maximum	55
Percentiles	
25	42.75
50	47.00
75	51.00

SD: Standard deviation, SEM: Standard error of mean

Table 2: Age-wise distribution of different types of the primary angle closure disease

Age group	Subtype		
	PACS	PAC	PACG
19–25	0	1	0
26–35	4	3	0
36–45	27	16	11
46–55	47	32	9
Total	78	52	20

PACS: Primary angle closure suspect, PACS: Primary angle closure, PACG: Primary angle closure glaucoma

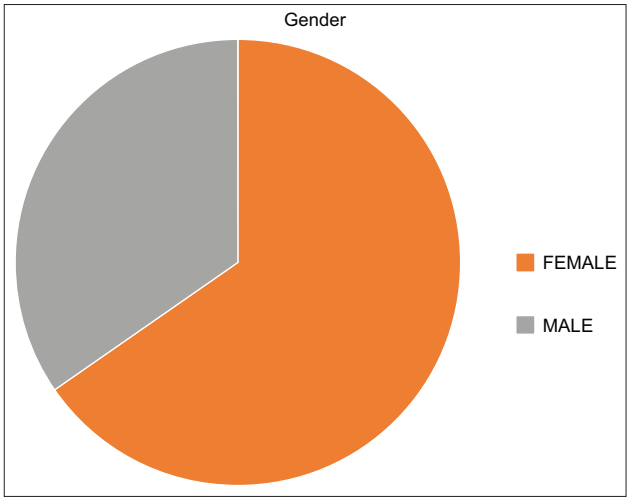

Figure 1: Gender distribution of the subjects

DISCUSSION

The estimated global prevalence of glaucoma was found to be 3.54% in a systematic meta-analysis in 2014,[11] with the highest prevalence in Africa. The prevalence of POAG is highest in Africa, while the prevalence of PACG is highest in Asia.

Several studies have shown that the prevalence of glaucoma increases with age. Our study also showed higher prevalence of glaucoma to be in the age group of 46–55 years, 58.6% of the total population were in this age group which is significantly higher. The Andhra Pradesh eye disease study also found that prevalence is 2.21% in 40 years and above patients and 1.41% in 30 years of age and older glaucoma patients.[11,12]

Our study shows a higher prevalence of glaucoma in female than male. The Aravind Comprehensive Eye Survey,[12] Barbados Eye Study,[13] Rotterdam Study,[14] and Framingham Eye Study[15] also showed a higher prevalence

of glaucoma in men, whereas the Beaver Dam Eye Study[16] showed no gender difference in glaucoma prevalence. The Blue Mountains Eye Study[16] Reported a higher prevalence of glaucoma in women.

The strength of this study was that it was conducted in a tertiary care hospital with all the standardized protocols and calibrated instruments among the patients in a randomized manner. However, the main limitation of this study was its less sample size and lack of routine follow-up due to various reasons.

CONCLUSION

This study determined the prevalence of angle closure glaucoma among the patients attending our hospital and found that PACS is the most common subtype of glaucoma, whereas PACG was found to be the least common. Females are generally more affected as compared to males.

Most of the patients that attended the outpatient department were asymptomatic with a chronic presentation.

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Original Article

Retrospective and Single-center Cohort Study to Determine Factors Affecting Perioperative Outcome in COVID Positive Women Underwent Cesarean Section

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Abstract

Aims and Objectives: The parturient physiologic state is significantly altered from non-pregnant women; COVID-19 adds more challenges in management of parturient as pregnancy increases susceptibility to respiratory complications. The aim of this study is to determine factors affecting perioperative outcome in COVID-19 positive pregnant women underwent cesarean section.

Materials and Methods: The retrospective and single-centered cohort study was carried out in the Department of Anesthesiology and Critical Care Medicine, M.L.B. M.C. a tertiary medical center in Jhansi (U.P.), in collaboration with the Department of Obstetrics and Gynecology, a total 55 patients of SARS COV-2 positive patient who underwent cesarean section were included in the study. Patient demographics and other informations were taken from the patient medical file and analyzed retrospectively.

Results: A total of 55 patients who were SARS-CoV-2 PCR tests positive were included in the study and further statistical analysis. The majority of the patient belong to 20–30-year age group (72%) and were unbooked (76.36%), the mean gestational age at delivery was 33–36 weeks (43.64%), Obesity was present in 2 (3.64%) patient, three patients were elder mother (5.45%). The majority of cesarean sections were due to fetal distress (58.18%) and were operated under spinal anesthesia (92.72%), mean arterial blood pressure was found 80–100, expect for the patient with sever disease, tachycardia was present in majority (90%) of the patient. Lymphopenia, thrombocytopenia, eosinophilia, neutrophilia, and leucopenia in general are some findings seen in most of the COVID-19 patients especially in ICU. General anesthesia given to 4 patients (7.27%), neonatal morbidity was seen as FGR (40%) and low APGAR score (80%), and need of NNU admission (80%), during the duration of study, there were 2 IUD (3.64%) and 4 maternal mortalities (7.27%) observed. Four anesthesia resident became positive involved in these operations.

Conclusion: COVID-19 is now considered more as a systemic infection rather than the common flu. Beside severe disease; obesity, elder maternal age, and primiparity were independent risk factors for poor outcome. The risk of transmission can be reduced with appropriate PPE and regional anesthesia.

Key words: Cesarean section, COVID-19, Pregnancy, SARS-COV-2

INTRODUCTION

SARS-CoV-2 causing COVID-19 disease spread all over the world, the World Health Organization (WHO) declares this easily spreading disease as global pandemic on March 11, 2020[1], as of current worldwide status while writing this paper, there were more than 462,410,883 coronavirus confirmed cases and approximately 6,075,665 deaths were reported, in which India contributing about 42,998,938 confirmed cases and 519,103 total deaths as per data updated by WHO (*covid19.who.int/table*).

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Perioperative management of parturient has always been considered challenging regarding difficult airways and pulmonary complications (decreased FRC and reactive airway) due to relatively depressed immunity and several

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cardiopulmonary changes during pregnancy[2]. Pregnant women are more prone to morbidity and mortality due to COVID-19 infection in comparison to non-pregnant female. Hematologic profiles depend on the severity of the disease. The major pregnancy-related hemodynamic changes include increased cardiac output, increase in blood volume, and decreased systemic vascular resistance and blood pressure[3]. A significant number of deaths due to COVID-19 infection can be attributed to cytokine storm and cytokine release syndrome. COVID-19 can exacerbate thrombophilia, due to a rise in D-dimer levels and longer PT[4,5].

In this study, our aim is to evaluate the demographic data of COVID-19 patients underwent cesarean section, our anesthesia technique, complications, and neonatal outcome.

MATERIALS AND METHODS

Study Design and Ethical Statement

The retrospective and single-centered cohort study was carried out in the Department of Anesthesiology and Critical Care Medicine, M.L.B. M.C. a tertiary medical center in Jhansi (U.P.), in collaboration with the Department of Obstetrics and Gynecology, data collected from patient medical file, operation theater register, and labor room register, after the approval of Institutional Ethical Committee.

A total 55 patients of SARS-CoV-2 positive patient who underwent cesarean section were included in the study. Patients who were clinically suspected (clinical symptoms or travel history), but tested negative for COVID-19 were excluded from the study. In our institute's protocol, we tested every patient for RAPID ANTIGEN, TRUNAAT, and RTPCR before taking emergency or routine cesarean section. Patient demographics and other informations were taken from the patient medical file and analyzed retrospectively.

Inclusion Criteria

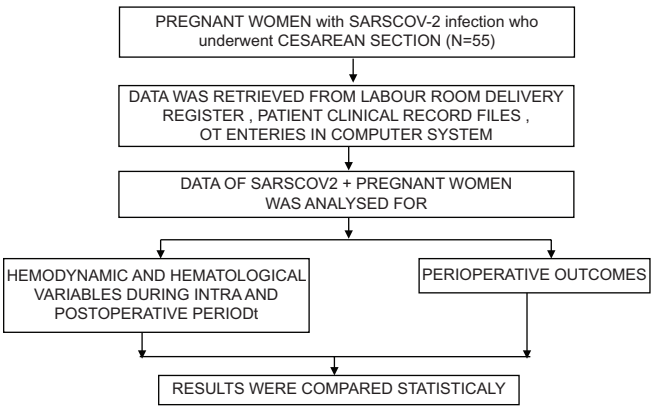
SARS-CoV-2 positive pregnant women of reproductive age group between 18 and 45 years belonging to ASA Grade I–IV, underwent cesarean section during COVID pandemic were included in the study.

Exclusion criteria

Records not trackable were excluded from the study.

Statistical analysis was performed with SPSS software 21 windows (statistical package for the social sciences). Categorical data were expressed in number (%), while continues data were expressed in mean (SD) percentage. Spearmen's correlation test was used for correlation analysis. The value <0.05 was considered statistically significant.

Consort Diagram



RESULTS

A total of 55 patients who were positive SARS-CoV-2 RTPCR were included in the study and further statistical analysis done. The majority of the patient belong to 20–30-year age group (72%) with mean age of studied population that was 29.65 ± 5.6 years and were electively operated for cesarean (76.36%), the mean gestational age at delivery was 35.36 ± 3.26 weeks. Mean BMI reported was 19 ± 3.25, with obesity in 2 (3.64%) patient, with, three patients were elder mother (5.45%). About 26 (50.90%) of the all patients not have any chronic medical illness, while pneumonia, anemia, and chronic hypertension gestational diabetes were the most common medical illness. The most of the patient belong to the ASA Grade II, but there were four patients belonging to ASA Grade IV, while two patients were already in mechanical ventilation support and were shifted to operation theatre with all precautions, the demographic distribution along with other baseline data is given in Table 1. Forty-two (76.36%) cases were recorded as emergency cases, the majority of cesarean sections were due to fetal distress (58.18%) and were operated under spinal anesthesia (92.72%).

The patient was preloaded with balanced crystalloid, ringer lactate 500 ml, before applying spinal, the subarachnoid block was performed by injecting 10 mg of 0.5% bupivacaine with 25G quincke spinal needle at L3-4 intervertibral space, mean arterial blood pressure was found 80–100 mmHg, while hypotension in 13 (25.49%) patient was recovered using injection ephedrine 7.5 ± 6.5 mg intravenously, there was no episode of vomiting, shivering, and failed spinal block in any of the patients. Expect for the patient with sever disease, tachycardia was present in majority (90%) of the patient. SpO_2 was significantly less for 6 (10.90%) patients. Lymphopenia, thrombocytopenia, eosinophilia, neutrophilia, and leukopenia in general are some findings seen in most of the COVID-19 patients especially in ICU as shown in Table 2. Although the majority of covid infected pregnant females were aymptomatic, amongst symptomatic the most frequent

symptom was cough followed by myalgia, sorethroat and headache. Oxygen therapy was required by as high as 14.54% of covid positive pregnant women as shown in Table 3.

42(76.36%) cases were recorded as emergency cases, Majority of caesarean sections were due to fetal distress (58.18%) and were operated under Spinal Anesthesia (92.72%), General Anesthesia given to only 4 (7.27%) patient shown in Table 4 in which two patients who were already on mechanical ventilation, and shifted to the operation theatre from ICU, one patient had platelet count 65000/mm^3, and one patient was unstable with severe pneumonia, in these four patients, there was no need to use injection ephedrine, In general anesthesia, we followed rapid sequence intubation using injection propofol and injection succinylcholine as induction agents, inj. Atracurium/oxygen/N_2O used as maintenance and injection fentanyl and sevoflurane was taken after cord clamping, only patient with thrombocytopenia was extubated with injection myopyrolate and shifted to ICU, while other three were shifted back to ICU on mechanical ventilation.

Table 1: Distribution according to the demographics and pre-operative data

Characteristics	*n*=55
Age (years), mean±SD	29.65±5.6
Gestational age, week, mean±SD	37.36±3.26
Basal metabolic rate (BMI)	19±3.25
Parity, *n* (%)	
Nulliparity	24 (43.63)
Multiparity	31 (56.62)
Medical history, *n* (%)	
No medical history	26 (50.90)
Pneumonia	12 (21.81)
Placental abnormality	5 (9.09)
Preeclampsia	3 (5.45)
Hypertension	4 (7.26)
Diabetes mellitus	2 (3.64)
Gestational diabetes mellitus	2 (03.63)
Thyroid disorder	1 (1.81)
Thrombophilia	1 (1.81)
Anemia	20 (36.36)
ASA grading, *n* (%)	
II	41 (74.54)
III	10 (18.18)
IV	4 (07.27)
Pulse oximetry, *n* (%)	
80	6 (10.90)
80–90	14 (25.45)
90–100	35 (63.63)

ASA: American Society of Anesthesiologists

Table 2: Distribution according to the laboratory variations

Hematological markers before surgery	Mean (*n*=55)±SD
Hemoglobin, g/dl	10.26±1.82
Platelet, mcl	206±62
Total leukocyte counts, cmm^3	5600±562.23
Aspartate aminotransferase, u/l	32±22.32
Alanine aminotransferase, u/l	27±23.12
Serum creatinine, g/dl	0.58±0.42
CRP	2.16±2.44
Normal Range – (lower than 1.0 mg/dl)	
Serum Ferritin	53.66±78.02
Normal Range – (11–150 ng/mL)	
D-dimer	3.00±2.24
Normal Range – (<5 ng/mL)	
Fibrinogen	456±144
Normal Range – (200–400 mg/dl)	

The requirement for post-operative ICU follow-up was 6 (10.90%) in all COVID-19 positive patients, 33.33% (6/18) in symptomatic patients and 50% (6/12) in pneumonia patients. Four maternal mortalities (7.27%) observed, while mortality rate in symptomatic patients was 22.22% (4/18) and 44.44% (4/9) in pneumonia patients.

The mean length of hospital stay was 7.92 ± 16.88 days. Two patient's length of hospital stay was longer than the other, 26–30 days, hemoglobin level has a negative correlation with length of hospital stay ($r = -0.263$ and $P = 0.05$), fibrinogen levels ($r = -0.322$ and $P = 0.009$), and the weeks of gestation ($r = -0.306$ and $P = 0.036$), there was positive correlation with age ($r = 0.286$ and $P = 0.0043$), there was no correlation between C-reactive protein, thrombocyte, lymphocyte, D-dimer, and ferritin level with length of hospital stay.

Neonatal morbidity was seen as FGR (40%), low APGAR score (50%), and need of NNU admission (26.42%), during the duration of study, there were 2 IUD (3.64%) as shown in Table 5. All two newborns are tested positive for COVID-19 with nasopharyngeal swab. All cesarean section was performed in operation room, reserved for COVID-19 patients, the whole team was equipped with Level-3 personal protective kit (PPE). Patients were transferred to the COVID-19 Wards or COVID ICU. Two health-care professional from anesthesia team and two health-care professional from surgery became positive involved in these operations.

DISCUSSION

COVID-19 is now considered more as a systemic infection rather than the common flu. Beside severe disease; obesity, elder maternal age, and primiparity were independent risk factors for poor outcome.

In this retrospective and observational study, we evaluated 55 COVID-19 positive parturient who underwent cesarean section during the epidemic period in our tertiary teaching institute, It appeared that COVID-19 does not causes impaired hemodynamic variables of patients. It is recommended to perform neura-axial anesthesia for COVID-19 positive patients when there is no

Table 3: Distribution according to the sign and symptoms of COVID-19 positive patients

Symptoms	Number *n* (%)
Asymptomatic	37 (67.27)
Symptomatic	18 (32.27)
Fever	6 (10.90)
Myalgia	8 (14.54)
Sore throat	6 (10.90)
Cough	9 (16.36)
Shortness of breath	5 (09.09)
Tiredness	5 (09.09)
Headache	6 (10.90)
Loss of taste and smell	4 (07.27)
Oxygen therapy	8 (14.54)

Table 4: Distribution according to the operative data and perioperative events

Characteristics	*n* (%)
Emergency	42 (76.36)
Elective	13 (23.63)
Mean arterial pressure	86.62±8.65
Heart rate	92±9.65
Indication for cesarean delivery	
Scar tenderness	12 (21.82)
Fetal distress	32 (58.18)
Obstructed labor	4 (07.27)
Cephalopelvic disproportion	3 (05.45)
Non-progress of labor	4 (07.27)
Type of anesthesia	
Spinal	51 (92.72)
General	4 (07.27)
Duration of surgery (minutes)	68±18.6
Blood loss (mL)	682±199.6
Fluid given (mL)	2172±642.2

contraindication.[6] Chen *et al.*[7] applied general anesthesia to three of 17 COVID-19 positive patients undergoing cesarean section and the remaining 14 patients received epidural anesthesia. While no hypotension was observed in the general anesthesia group; the hypotension rate was as high as 86% in the epidural group.[7] In this study, four of 55 patients were given general anesthesia, use of ephedrine was not required in patient who underwent general anesthesia. The rate of spinal anesthesia was 92.72% and requirement of ephedrine was 25.49%. In the study of Chen *et al.*,[7] all of the patients undergoing general anesthesia were emergency patients while the epidural group consisted of elective patients. In our study, 42 (76.36%) of the cases were emergency patients.

The previous studies show that the most obstetric patients were asymptomatic at the time of admission or had COVID-19-like symptoms (fatigue, muscle pain, shortness of breath, congestion, etc.), which can be easily confused with common pregnancy symptoms. In this study, 67.27% of our COVID-19 positive patients included were asymptomatic.

Table 5: Distribution according to the neonatal outcome

Neonatal outcome	Number (%)
Neonatal complications	
FGR	22 (40)
Oligohydramnios	32 (58.18)
Preterm	2 (3.64)
IUD	2 (3.64)
Gender	
M	24 (43.63)
F	31 (56.36)
APGAR	
At birth	
≤7	28 (50.90)
8–10	27 (49)
At 5 min	
≤7	20 (36.36)
8–10	35 (63.63)
Birth weight	
Normal	35 (63.63)
Low	17 (30.90)
Very low	2 (3.63)
Extremely low	1 (1.82)
Umbilical cord pH	
7.20–7.38	52 (94.94)
<7.20	3 (5.45)
NICU admission	14 (26.42)

In our study, maternal mortalities rate was 7.27%, while mortality rate in symptomatic patients was 22.22% (4/18) and 44.44% (4/9) in pneumonia patients. Juan *et al.*[8] reported seven maternal deaths in a review of 324 pregnant women with COVID-19 infection and reported the frequency of serious pneumonia in pregnant women as 0–14%. In the study of Chen *et al.*,[7] one of the first articles on pregnant women at the beginning of the pandemic, all patients had chest tomography scans, in which all were compatible with pneumonia. In our study, rate of pneumonia was 21.81%, in all patients, while in symptomatic patients, it was 66%.

Chen *et al.*[7] emphasized that 14 patients had a hospital stay of 6–13 days. In our study, the length of hospital stay was found as 7.92 ± 16.88 days. In our study, we found a significant negative correlation with hemoglobin levels, fibrinogen levels, and gestational week for the length of hospital stay and a significant positive correlation with age.

Schwartz[9] reported that comorbid diseases (pre-eclampsia, pregnancy-induced hypertension, gestational diabetes, uterine atony, etc.) do not pose a risk for intrauterine transmission SARS-CoV-2 to the fetus. They also found no association between 30 and 40 weeks of gestation and mother-to-child transmission. Juan *et al.*[7] reported four intrauterine fetal deaths and two neonatal deaths in their systematic review. Two COVID-19 infections and no congenital anomaly were detected in any of our newborns. Of these newborns, 26.42% needed neonatal intensive care.

Lucas *et al.*[10] obstetric anesthesia experiences in COVID-19 reported that the most of the transmissions could be prevented by wearing and removing PPE correctly. Furthermore, in our study, all anesthetists used Level-3 PPE and two of them became infected afterward. The lower incident of infection in anesthetists performing cesarean section indicates that the risk of transmission can be reduced with appropriate PPE and regional anesthesia.

There is currently no evidence for intrauterine infection caused by vertical transmission in women who develop COVID-19 pneumonia in late pregnancy[11],also in our study only 2 newborns were tested positive for covid-19 with nasopharyngeal swab.

Karaca *et al*[12] General anesthesia was applied to only three patients (4.9%), while spinal anesthesia was administered to the remaining 58 patients (95.1%). Forty-one (67.2%) parturients were asymptomatic. While the rate of pneumonia in symptomatic patients was 45% (9/20), the pneumonia incidence among all SARS-CoV-2 PCR (+) parturients was 14% (9/ 61).They concluded that Spinal anesthesia was safely and effectively administered in COVID-19 parturients, especially in patients with pneumonia, also in our study, majority of caesarean sections were due to fetal distress (58.18%) and were operated under Spinal Anesthesia (92.72%), General Anesthesia given to only 4 (7.27%). 67.27% of the parturients were asymptomatic, while the rate of pneumonia in parturients was 21.81%, majority were operated under spinal anesthesia. Karaca et al observed that overall mortality rate was 1.6% (1/61) among parturients with COVID-19 undergoing cesarean section, while it was 11.1% (1/9) in patients with pneumonia. However in our study 4 maternal mortalities (7.27%) observed, while mortality rate in symptomatic patients was 22.22%(4/18) and 44.44%(4/9) in pneumonia patients.

Limitations

It was a single-center study, we could include more centers for better interpretation of data, RTPCR testing limitations also played important role in undervaluation of COVID-19 cases. The treatment guidelines were also evolving; hence, change in treatment guidelines has an impact on the length of hospital stays, as home treatment implemented as the pandemic progressed.

There are very literature available about COVID-19 patient, our study oriented toward the anesthesia experiences in COVID-19 positive parturient; hence, further studies needed for understanding this disease.

CONCLUSION

COVID-19 is now considered more as a systemic infection rather than the common flu. Beside severe disease; obesity, elder maternal age, and primiparity were independent risk factors for poor outcome. The risk of transmission can be reduced with appropriate PPE and regional anesthesia.

AUTHOR CONTRIBUTIONS

Conceptualization, Methodology, Validation and Supervision, Dr. Shivali Pandey; Investigation, Data Curation, Writing-Original Draft Preparation, Dr. Anil Kumar, review and editing Dr. Yamuna.

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Original Article

Nutrition in Total Knee Arthroplasty and its Functional Outcomes in Vegetarians Population Compared to Non-vegetarians in Indian Scenario – A Prospective Study

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Abstract

Purpose: The main objective of the study is to compare the functional results in the vegetarian population compared to the non-vegetarian population in patients with total knee Arthroplasty (TKA).

Material and Method: We performed a prospective analytic study between 2017 and 2018 to compare the functional outcome between the vegetarian population and non-vegetarians undergoing TKA at 3-year follow-up, Measurement results include knee society score (KSS) and oxford score.

Results: A total of 200 patients who underwent primary TKA were evaluated, of which 100 were vegetarians (Group A) and 100 were non-vegetarians (Group B). At the time of the latest follow-up (minimum 3 years), KSS score was non-significant between the two groups (pre-operative KSS score 75.59 ± 12.75 in Group A vs. 75.55 ± 12.78 in Group B) and post-operative KSS score 156.51 ± 8.74 in Group A versus 157.50 ± 8.71 in Group B ($P = 0.41$). Functional outcomes were measured in terms of oxford knee score (OKS) for patients undergoing primary TKA. In vegetarians (Group A), OKS was mean 41.27 ± 2.56 and 43.31 ± 1.06 in the non-vegetarian (Group B) population at 3-year post-operative follow-up period. There was a statistically significant difference between the two groups in terms of functional outcome ($P < 0.001$).

Conclusion: The prospective analysis demonstrated that the functional outcomes of primary TKA in a vegetarian population (Group A) post-operative period were lower when compared to that in non-vegetarian.

Key words: Arthroplasty, Diet, Nutrition, Vegetarian

INTRODUCTION

Vegetarians are generally defined as people who do not eat any kind of meat, poultry, or fish.[1] The popularity of vegetarianism worldwide varies greatly from 0% to 42%, determined by, civilization, outsourcing, and another aspect,[2,3] but it implies that vegetarian diets are flourishing globally.[4] In contrast, a large portion (35%) of the Indian population is vegetarian.[5] Vegetarians may be at increased risk for deficiencies in Vitamin B12, iron, calcium, Vitamin D, omega-3 fatty acids, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and protein.[5,6] Despite some benefits, vegetarians could be at risk for deficiency of essential nutrients, hence, affecting the outcome in patients undergoing primary total knee arthroplasty (TKA). Plant foods contain a negligible quantity of Vitamin B12; so, vegetarians have issues meeting the recommended daily allowance (2.4 μg) and maintaining a concentration of serum B12 adequately.[7]

While overall iron intake was surprisingly higher in vegetarians than in omnivores, levels of ferritin and an iron storehouse were generally lower in vegetarians. Vegetarians occasionally have much lower Ca levels unless they eat a

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lot of Ca rich plant foods like dark green vegetables. Many researches have documented decrease consumption of calcium and intake of Vitamin D in vegetarians, but the consequences of a vegetarian food regimen plan on bone health, particularly bone mineral density (BMD), have been varied.[8]. Many studies have proven decrease BMD in vegetarians in comparison with non-vegetarians. Two important fatty acids have to be non-inheritable in the food plan as a human body cannot synthesize them: Linoleic acid (LA) and α-linolenic acid (ALA).[9] Two other fatty acids which might be lacking in vegetarian diets are EPA and DHA. Plant assets are often considered incomplete sources of protein and lack at least one essential amino acid.

In recent years, the sector of nutrition applied to orthopedics has developed, with the requirement to boost the potency of the treatment path by enhancing the recovery when surgery.[10] One major aspect of the field is that the undeniable fact that orthopedical surgery (e.g., knee/hip replacement and spine surgery) finds its typical candidate to be an aged individual ordinarily stricken by pathology and cardiac disease. With aging, nutrition plays a big role in maintaining physical and psychological feature skills.[11,12] Similarly, organic process standing can have a consequence on the surgical outcome of patients undergoing major surgery, particularly the seniors with restricted practical reserves.[13] Surgery is a stressful event that ends up in a pro-catabolic hormonal secretion and cytokine environment, which significantly impacts the metabolism. This metabolic response is accompanied by the high levels of oxidative stress, hyper inflammation, and immune system impairment, increasing the risk of post-operative complications.[14] Often as a result of pre-surgery immobilization due to pain, orthopedic patients will suffer muscle disuse atrophy. It is thought that increasing protein consumption in the elderly can maintain lean body mass and function.[15] According to the reports, vital amino acids can enhance the body and its capacity to synthesize protein and restore muscles. This can provide patients with greater functional reserves to better withstand surgical pressure.

Purpose of Study

The primary objective of the study was the functional outcome in vegetarian and non-vegetarian TKA patients. We hypothesized that the vegetarian diet population has less functional scores and range of motion as compared to the non-vegetarian group population.

MATERIALS AND METHODS

The study design is a prospective and single-center trial adhering to Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) guidelines. The study carried out at our tertiary hospital specializing in joint replacement surgery. This study was designed to compare the functional outcome in vegetarian versus non-vegetarian patients undergoing TKA from 2017 to 2018 at our facility. Each patient in the study had to undergo TKA through a unique technique by a single surgeon. This study received Institutional Research Board approval. Inclusion criteria subject with Grade 4 knee osteoarthritis patients with strict vegetarians (Lacto-vegetarian) and not consuming meat and egg product and who had undergone primary TKA that could not be treated conservatively. Subjects also had to have a varus/valgus deformity that matched within 5° of other groups assessed using knee society score (KSS). Exclusion standards – a flexion contracture more than 15°, any extra-articular knee deformities, and with inflammatory arthritis to reduce the bias on outcome. Pre-operative demographic data were recorded for all subjects, including height, weight, age, comorbidities, hemoglobin, serum albumin, Vitamin D3 level, gender, and pre-operative deformity using KSS. Pre-operative radiographs were obtained for all subjects and included a standing full-length anterior-posterior (AP) view that spanned from the hip joint to the ankle joint. Functional evaluation was measured with the oxford knee score (OKS) at time of pre-operative assessment and at 3-year follow-up visit and compared with non-vegetarians patients undergoing TKA during the same period. Both groups were matched to reduce the influence of demographic characteristics on the results of the study. The patients were divided into two groups and willing to follow-up regularly:

(1) Group A – vegetarians patients undergoing TKA ($n = 100$)
(2) Group B – Non- vegetarians patients corresponding to Group 1 ($n = 100$)

All data are collected by the research fellow.

Post-operative Care

All patients received the same standardized post-operative multimodal pain protocol, with three doses of 1 g of acetaminophen, two doses of IV antibiotics, and morphine or tramadol for pain exacerbations. All patients underwent the same post-operative rehabilitation program, with full weight-bearing with the use of a walker from the 1st post-operative day and active range of movement exercises. DVT prophylaxis was given in all patients.

Outcome Evaluation

Outcome measures included the OKS, KSS, and the range of movement assessment. The scores were recorded before surgery and postoperatively scores at 3 years of follow-up. The range of motion is recorded through a goniometer.

Statistical Analysis

Data have accumulated with the use of a semi-dependent pre-tested questionnaire, records collected were entered in Microsoft Excel 2013. Data are represented in frequencies

and percentages, charts, and graphs. The mean and standard deviation of quantitative variables are shown. Appropriate statistical assessments have been implemented with the use of the SPSS software program model 21 for analysis. The Chi-square test is used for affiliation and the student's *t*-test is used for evaluation among the study variables. Statistical significance is considered at $P < 0.05$.

RESULTS

In this study, a total of 200 patients who underwent primary TKA were evaluated, of which 100 were vegetarians (Group A) and 100 were non-vegetarians (Group B). Female predominance in each group (83 in Group A vs. 76 in Group B) (Table 1, $P = 0.22$) with the mean age group is 58.37 ± 2.15 (A) and 57.99 ± 2.16 (B), mean BMI of patients in Group A is 22.98 ± 5.67 and Group B is 23.45 ± 4.76, Charlson comorbidity index is 1.39 in Group A and 1.38 in Group B, pre-operative HB in Group A 12.20 ± 0.86 versus 12.15 ± 0.99 in Group B and post-operative HB 10.40 ± 1.03 in Group A versus 10.44 ± 1.02 in Group B [Table 2] were followed up at the very least 3 years with no statistically significant difference among the two groups ($P > 0.005$). At the end of the final follow-up, implant survivorship was 100% for both groups with no revision surgery performed for any indication. Serum albumin mean was 3.21 ± 0.39 in Group A versus 3.39 ± 0.30 in Group B ($P < 0.001$) significant between two groups, serum Vitamin D3 mean in Group A is 27.65 ± 5.23 versus 42.46 ± 14.44 in Group B ($P < 0.001$) which is significant difference between two groups. KSS score was non-significant between two groups (pre-operative KSS score 75.59 ± 12.75 in Group A vs. 75.55 ± 12.78 in Group B) and post-operative KSS score 156.51 ± 8.74 in Group A versus 157.50 ± 8.71 in Group B ($P = 0.41$). Functional outcomes were measured in terms of OKS for patients undergoing primary TKA. In a vegetarians (Group A), OKS was mean 41.27 ± 2.56 and 43.31 ± 1.06 in non-vegetarian (Group B) population at post-operative 3-year follow-up period. There was a statistical significant difference between two groups in terms of functional outcome ($P < 0.001$) [Table 3].

Complications

There were no reoperations in this study series over the 3-year follow-up span. There were no wound complications further requiring additional oral or intravenous antibiotics. At the 3-year follow-up, there have been no cases of chronic periprosthetic joint infection. Two subjects were asked to manipulate the stiff knee joint under anesthesia. One subject in Group A is a vegetarian and one subject in Group B. is not a vegetarian [Figures 1 and 2].

Table 1: Gender distribution

	Veg	Non-Veg	Total
F	83	76	159
M	17	24	41
Total	100	100	200

Table 2 : Different demographics study parameters comparison in groups

	Group	Mean	Std. deviation	*P* value
BMI	Veg	22.98	5.67	0.98
	Non-veg	23.45	4.76	
Age	Veg	58.37	2.15	0.21
	Non-veg	57.99	2.16	
Charlson comorbidity index	Veg	1.39	0.78	0.92
	Non-veg	1.38	0.71	
Pre-operative HB	Veg	12.20	0.86	0.69
	Non-veg	12.15	0.99	
Post-operative HB	Veg	10.40	1.03	0.77
	Non-veg	10.44	1.02	
Serum Albumin	Veg	3.21	0.39	<0.001
	Non-veg	3.39	0.30	S*
Vitamin D	Veg	27.65	5.23	<0.001
	Non-veg	42.46	14.44	S*

S*: Significant Difference

Table 3: Different study parameters comparison in groups

Group	Mean	Std. deviation	*P* value
Pre-operative Knee Society Score			
Veg	75.59	12.78	0.98
Non-veg	75.55	12.95	NS
Post-operative Knee Society Score			
Veg	140.91	17.38	0.0001
Non-veg	157.51	8.71	NS
Oxford Knee Score			
Veg	41.27	2.56	<0.001
Non Veg	43.31	1.06	S*

S*: Significant Difference

DISCUSSION

Total knee replacement (TKR), one of the frequently performed orthopedic surgeries, and as the number of procedures increase as population ages, the nutrition should be considered for its role in the management of stress responses during surgery, as the need for early recovery and return to function after surgery increases with the increase in active aging. TKR is a stress stimulus that has profound effects on metabolism from the environment of metabolic hormones and cytokines. This is associated with the high levels of oxidative stress, hyper inflammation, and changes in the immune system, which increase the risk complications after surgery.

Orthopedic patients show severe muscle atrophy due to pre-operative pain-related fixation. Therefore, it has been

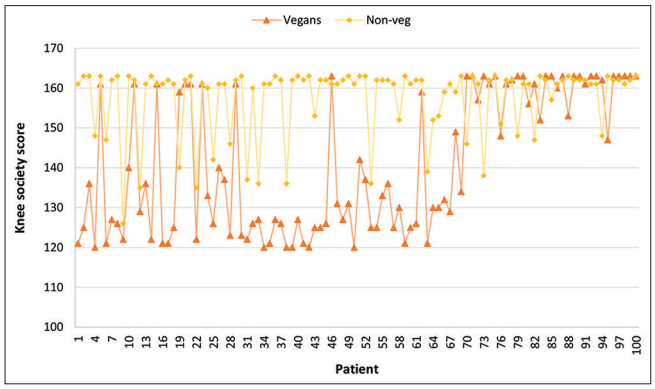

Figure 1: Knee society score

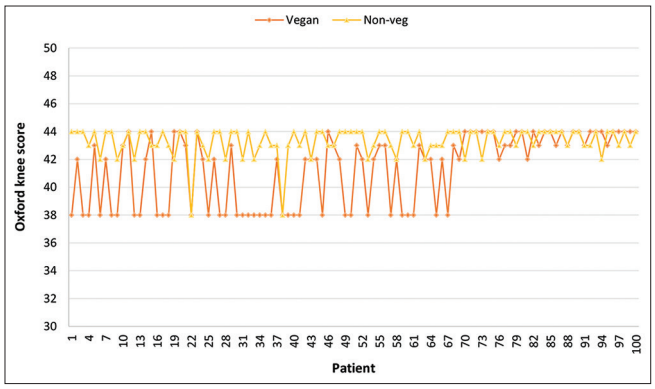

Figure 2: Oxford knee score

suggested that increasing protein intake in the elderly can maintain lean body mass and function.[15,16] Essential amino acids are recognized to boom the body's capacity to synthesize proteins and restore muscle tissue.[17] The richest source of essential amino acids is meat and meat products, which are not consumed by vegetarians and therefore affect their functional outcomes and early mobilization.

Serum cholesterol and blood pressure have a normal range in vegetarians, reducing the risk of cardiovascular disease. BMD, and therefore the risk of fractures, may also be a priority if intake of calcium and Vitamin D is insufficient. In our study, we found that functional OKS outcomes were statistically significant in non-vegetarian patients compared with vegetarian patients at 3 years of follow-up. Likewise, serum albumin and serum Vitamin D levels were statistically significant in the non-vegetarian group compared with the vegetarian group. This could be a confounding factor for the difference in functional outcome between the two groups. Chiu *et al.*[18] summarized in their study that variable causes bone loss in postmenopausal Taiwanese vegetarians. Fortified food with calcium and Vitamin D should be taken whenever available. Vitamin B12 deficiency can be a potential problem for vegetarians, so it is imperative to take foods or supplements fortified with Vitamin B12. To optimize vegetarian status in n-3 fatty acids, you should regularly consume foods rich in ALA, foods fortified with DHA, or foods fortified with DHA. In general, vegetarians can avoid nutritional health problems by choosing the right food.

Tuckert *et al.*[19] found that vegetarians may be at increased risk of the lower BMD and fractures, which indirectly affect bone strength and functional outcomes. Lavernia[20] concluded the impact on post-operative results as vegetarians do not consume a high source of animal protein that indirectly contributes to the body's production of albumin, which is necessary for the healing process, and thus nutrition for the consequences in arthroplasty. Following the conclusion of Maniar *et al.*,[21] Vitamin D deficiency adversely affects the functioning of patients with knee osteoarthritis with low Vitamin D content, it also affects post-TKR results.

Post-operative recuperation is multifactorial[22] and the function of inflammatory/immune responses before and after surgery is a critical element in decreasing rehabilitation, post-operative pain, and malaise. It is important. Therefore, in the case of joint replacement, the predisposition to pre-operative localized myositis at the time of surgery may be an important consideration for post-operative recovery.[23] Polyunsaturated n3 fatty acids (PUFAs) can help regulate the main inflammatory pathway[24] and reduce pre-operative inflammatory burden, which can accelerate recovery. The main source of PUFA (EPA and arachidonic acid) is found in animal fats and fish not consumed by vegetarians.

In our research, the functional outcomes of non-vegetarians were relatively good in comparison to the vegetarian population after the primary TKA, and also patients in non-vegetarian group have statistically significant difference in terms of pre-operative serum albumin and serum Vitamin D3 compared to vegetarian group, but more research must be done and longer follow-up is obligatory to judge the outcomes in both groups.

It is recommended that some supplements may play a role in bettering the recovery of patients undergoing TKR. The constraint of study was small sample size, early follow-up, and no consideration was given to the interpretation of albumin and other nutritional parameters. To the best of our knowledge, there is no documented previous study comparing these two groups in knee replacement surgery.

CONCLUSION

Functional results of primary TKA in the vegetarian population are lower to non-vegetarian groups during the post-treatment period (3 years after initiation). Compared

to non-vegetarians, vegetarian candidates appear to have health and nutritional deficiencies, lower Vitamin D storage, and serum albumin/protein levels. TKA in vegetarian patients needs to be provided with cautious nutritional planning and supplementation. Future studies of TKA patients are warranted within side the context of nutritional preferences.

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Original Article

Functional Endoscopic Sinus Surgery Nasal Irrigation with Budesonide: Quality of Life Assessment in Chronic Rhinosinusitis Patients

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Abstract

Introduction: Chronic rhinosinusitis (CRS) not responding to medical treatment is managed by functional endoscopic sinus surgery (FESS) followed by steroid nasal spray. CRS significantly affects the quality of life of patients. Saline nasal irrigation is recommended after sinus surgery. Off label addition of budesonide respules in saline irrigation solution is reported to beneficial for even distribution of steroid in opened sinuses.

Materials and Methods: The study was conducted in CRS patients who had undergone FESS. Normal saline with budesonide nasal irrigation was advised and the effect on the quality of life was determined using the Sino-nasal Outcome Test-22 (SNOT-22). Total 50 cases were studied. Pre-operative computed tomography scans were obtained and assessed by Lund-Mackay scoring. Rigid sinonasal endoscopy was performed and modified Lund-Kennedy endoscopy scale score calculated. Visual analog scoring and SNOT-22 questionnaire scoring were done preoperatively and at 3rd-and 6th-month postoperatively. These scores were compared and a value of $P < 0.05$ was considered statistical significant.

Results: Nasal blockage was the most common symptom followed by rhinorrhea. Maximum pre-operative SNOT-22 scores were of nasal blockage (4.24 ± 1.94), runny nose (3.74 ± 1.747), and facial pain (3.44 ± 1.567). The mean pre-operative SNOT-22 score was 43.56 ± 18.33. The average number of total nasal irrigation performed was 72.54 ± 10.73. After FESS, following patients reported improvement in visual analog scale and SNOT-22 scores.

Conclusion: In refractory CRS, patients' symptom score improved after FESS and steroid saline irrigation. Good compliance achieved for nasal irrigation after counseling, demonstration, and continuous motivation.

Key words: Budesonide nasal wash, Chronic rhinosinusitis, Functional endoscopic sinus surgery, Nasal douching, Sino nasal outcome test-22, SNOT-22

INTRODUCTION

Chronic rhinosinusitis (CRS) is defined by European position paper on rhinosinusitis and nasal polyposis (EPOS) as inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage or nasal discharge in addition to facial pain/pressure and/or reduction of smell, lasting for at least 12 weeks.[1] CRS is essentially a medical disease; however, in cases not responding to medical treatment surgery is indicated which includes functional endoscopic sinus surgery (FESS) which is performed to minimally remove the inflamed mucosa and restore the ciliary transport mechanism and mucous clearance pathway.[2]

Saline nasal irrigation or nasal douche or lavage is a procedure that rinses the nasal cavity with isotonic or hypertonic saline solutions. Saline irrigation is highly recommended for medical and post-operative management of CRS without nasal polyposis in adults as well as children.

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Normal saline is also very commonly advised as an adjuvant for acute and chronic upper respiratory tract infections in infants and children. Normal saline is a physiological solution and it cleanses the nasal mucosa and improves mucociliary action by removing nasal crust and by thinning the mucous. There by saline irrigation helps in decreasing the infection and allergen load resulting in decreased inflammation and edema.[3,4]

Topical steroid is highly recommended as first line treatment for CRS with or without nasal polyposis for medical management and postoperatively in adults. Usually, topical nasal sprays are prescribed for variable period after surgery.[1] Transnasal nebulization has been proved more efficacious in comparison to nasal spray in the management of CRS.[5] Delivery of steroid by nasal irrigation with high pressure has been recommended as a better option for treating chronic sinus mucosal inflammation as it leads to better penetration of steroids in sinuses and has anti-inflammatory action.[6,7]

Budesonide is approved to be used in nasal spray form and respules form for nebulization. Early evidence outlined suggests that budesonide irrigations provide benefit to patients with CRS following FESS and short-term use of topical high volume budesonide sinonasal irrigations is likely to be safe.[7] The study was conducted with the aim of assessing clinical outcome and quality of life in patients with CRS after nasal irrigation using normal saline with budesonide after FESS.

MATERIALS AND METHODS

The prospective study was carried out in the Department of Otorhinolaryngology, JLN Medical College and Hospital, Ajmer, from April 1, 2018 to March 31, 2019. Approval from the Institutional Ethics Committee was obtained. The study included cases fulfilling criteria of CRS diagnosed according to the European position paper on rhinosinusitis and nasal polyps EPOS 2012; characteristic changes in pre-operative computed tomography of paranasal sinuses assessed according to the EPOS 2012; CRS patients with bilateral nasal polyps and without nasal polyps who had not improved after medical treatment.[1] Other subgroups of CRS; secondary CRS; age <18 years; pregnant; immunodeficient; and patients undergoing revision FESS were excluded from our study group. The trial was registered with clinical trial registry of India CTRI/2019/02/017402. All procedures performed in the presented study involving human participants were in accordance with the ethical standards of the Institutional Ethical Committee of JLN Medical College Ajmer (Letter no. 2370/Acad-III/MCA/2016) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Target population for the study comprised of patients of CRS described as above not responding to medical management for a period of 3 months. Total 50 cases were included in our study group. Voluntary and informed consent was obtained from all study participants at the initial enrollment meeting. Written informed consent was obtained from all individual participants in native language. A detailed history was taken with special reference to age, sex, residence, occupation, family history, past history, allergic disorders, and any addictive habits. Detailed clinical examination local and general was made according to the proforma attached with special reference to nose and paranasal sinuses. Demographic data were recorded as well as associated medical comorbidities, including presence of nasal polyposis, asthma, allergies, prior sinus surgery, and treatment history. These cases were subjected to routine biochemical and hematological evaluation. Pre-operative computed tomography scans in the coronal plane were obtained and assessed by Lund-Mackay scoring (score range: 0–24).[8] Rigid sinonasal endoscopy was performed and graded according to the modified Lund-Kennedy endoscopy scale (LKES) (score range: 0–20) and Sino-nasal Outcome Test-22 (SNOT-22) was measured.[9] Endoscopic sinus surgery was then scheduled and performed in accordance with established functional principles. FESS was performed under general anesthesia, the surgical technique as described by Messerklinger.[10] The extent of surgery included at least a bilateral uncinectomy, middle meatal antrostomy with anterior ethmoidectomy. Septoplasty and/or inferior turbinoplasty were performed when indicated. Standard nasal packing (Merocel) was done for 48–72 h. Post-operative care was as follows: All patients received amoxicillin and clavulanic acid (875 mg/125 mg) twice a day for 10 days. After surgery, patients were instructed to begin nasal saline irrigations 48-72 h following surgery. Patients were instructed to irrigate with 240 ml normal saline, at least twice a day. Topical steroid irrigation was performed by adding one ampule having 0.5 mg/2 ml budesonide solution twice daily. Patients' noted the time, number, and amount of nasal irrigation in a proforma and submitted the proforma and empty respules every 15 day. Compliance to nasal saline irrigation instructions was defined as irrigation with 120 mL of normal saline per side, twice a day. Each patient was followed for four post-operative clinic visits at approximately 2 weeks, 4 weeks, 6 weeks, and 8 weeks after surgery.

Quality of life was assessed by SNOT-22 questionnaire and the symptom intensity was presented using visual analog score. Patients rate 22 questions from 0 (no problem) to 5 (problem is as bad as it can be). Lund Kennedy Endoscopic

scoring system (diagnostic nasal endoscopy) was used for signs of polyps, mucopurulent discharge primarily from middle meatus and/or edema/mucosal obstruction, scarring, and crusting preoperatively and postoperatively. The maximum score was 20 and the minimum score was 0.

The primary aim of the statistical analysis was to determine whether the changes of SNOT-22 scores, we had compared continuous variables using one-way analysis of variance tests and we used Pearson's χ^2 test to compare categorical variables. We then summarized the means of SNOT-22 scores before FESS, 3 months, and 6 months after FESS in CRS patients and the changes of SNOT-22 scores from pre-FESS to, 3-month, and 6-month post-FESS visits in CRS patients.

RESULTS

A total of 59 cases were recruited during the study period of which nine cases were excluded from the study. Demographic and clinical data of the study group are shown in Table 1.

Majority patients were <30 years. There were more males than females in the study group. Nasal blockage was the most common symptom followed by rhinorrhea. The symptoms of patients were scored based on visual analog score where 46 patients reported their symptoms as annoying or uncomfortable, while four patients as dreadful. Out of 50 patients, 32 were associated with allergy and nasal polyps and four patients had asthma. Twenty-one patients had deviated nasal symptom. Scores of SNOT-22 were given 0–5 for each symptom depending on the severity. Maximum SNOT-22 scores were of nasal blockage (4.24 ± 1.94), runny nose (3.74 ± 1.747), and facial pain (3.44 ± 1.567). The mean total TEC was 456.2 ± 181.23 per cubic mm and mean serum IgE was 151.97 ± 151.6.

Table 1: Demographic characteristics of study population

variables	Frequency (*n*=50)	Percent
Gender		
Female	19	38
Male	31	62
Age distribution		
<30 years	18	36
30–40 years	10	20
40–50 years	12	24
>50 years	10	20
Mean±SD	39.92±15.08	
Rural/Urban		
Rural	24	48
Urban	26	52

Average visual analog scale (VAS) scores for nasal obstruction, discharge, reduction of smell, and facial pain showed significant and sustainable post-operative improvement at 6 months after surgery ($P < 0.01$) [Table 2].

Mean pre-operative total SNOT-22 was 43.56 ± 18.33. Five patients showed nasal polyps at follow-up at 5–7-month postoperatively. The pre-operative mean total score on diagnostic nasal endoscopy was 8.26 ± 3.65 [Table 3].

Maximum patients (n = 41) performed nasal irrigation between 21 and 30 times at 2 weeks follow-up. The mean of total nasal irrigation performed was 72.54 ± 10.73.

Table 2: Pre-operative and post-operative mean total visual analogue scale scorer

Parameters	Baseline (Mean±SD)	At 6 months (Mean±SD)	*P*-value
Nasal obstruction	4.28±1.294	2.98±0.742	<0.01
Nasal discharge	2.12±1.92	0.00±0.00	<0.01
Reduction or loss of smell	2.34±1.507	1.78±0.764	<0.01
Facial pain/Pressure	3.44±1.56	2.84±1.434	<0.01

Table 3: Comparison of pre-operative and 3rd- and 6th-month post-operative mean diagnostic nasal endoscopy scoring

Parameter	DNE score	Mean	Std. Deviation	Significance of change with preoperative (*P*-value)
Polyp	Pre-operative	2.06	1.284	
	Post-operative 3rd month	0.12	0.328	<0.01
	Post-operative 6th month	0.10	0.303	<0.01
Discharge	Pre-operative	3.38	1.028	
	Post-operative 3rd month	0.38	0.567	<0.01
	Post-operative 6th month	0.16	0.370	<0.01
Scarring	Pre-operative	0.00	0.00	
	Post-operative 3rd month	0.84	0.866	<0.01
	Post-operative 6th month	0.70	0.909	<0.01
Crusting	Pre-operative	0.00	0.00	
	Post-operative 3rd month	1.56	0.675	<0.01
	Post-operative 6th month	1.72	0.536	<0.01
Edema	Pre-operative	0.00	0.00	
	Post-operative 3rd month	1.56	0.675	<0.01
	Post-operative 6th month	1.72	0.536	<0.01
Total	Pre-operative	8.26	3.658	
	Post-operative 3rd month	2.80	1.678	<0.01
	Post-operative 6th month	2.76	1.623	<0.01

DNE: stands for Diagnostic nasal endoscopy

Post-operative significant improvement of headache and all the symptoms of CRS was seen in those undergoing higher number of budesonide nasal irrigation and less crusting and synechiae formation was seen. Mean post-operative total SNOT-22 score after 3 months 14.42 ± 4.717 ($P < 0.01$) and after 6 months was 21.82 ± 7.819 ($P < 0.01$) [Figure 1].

The post-operative mean total score of diagnostic nasal endoscopy after 3 months and 6 months postoperatively was 2.80 ± 1.68 ($P < 0.01$) and 2.76 ± 1.62 ($P < 0.01$) [Table 3].

DISCUSSION

The present study was designed to evaluate and compare the quality of life in patients of CRS before and after FESS by SNOT-22. The study was conducted on the patients of CRS with or without nasal polyposis. The diagnosis of CRS was based on the definition of the EPOS 2012.[1]

In presented study, we enrolled 59 patients aged between 15 and 60 years of age. Out of 59 patients, nine patients were excluded from the study. Ling *et al.* reported average age of 49.4 (range 18–80) with a male-female ratio of 1:1.1.[11] Out of 50 patients, 9 (18%) were smokers. In the study of Gray *et al.*, 25.7% were smokers.[12]

Nasal obstruction was the most commonly reported disabling condition, reported in 42 (84%) patients, followed by rhinorrhea in 40 patients (80%), headache in 39 patients (78%), facial pain in 39 patients (78%), sneezing in 38 patients (76%), and hyposmia in 15 patients (30%). The study by Shivakumar *et al.* showed the most common symptom as nasal block (86.66%), followed by anosmia (77.14%), facial pressure (73.33%), postnasal drip (70.47%), headache (62.85%), nasal discharge (58.09%), fatigue (30.47%), halitosis (26.66%), dry cough (11.42%), dental pain (10.4%), and earache/fullness (6.66%).[2]

The mean of nasal irrigations (2-week, 4-week, 6-week, and 8-week follow-up) was 72.54 ± 10.73. Total ($n = 41$) patients had done nasal irrigation between 21 and 30 times at 2 weeks follow-up. Significant improvement in CRS symptoms was seen postoperatively in patients with higher compliance of budesonide nasal irrigation. Average VAS scores for nasal obstruction, nasal discharge, sneezing, and facial pain/pressure showed significant and sustainable post-operative improvement at 6 months after surgery ($P < 0.001$). Similar results have been reported by Soler *et al.* and Mace *et al.*[13,14]

The mean diagnostic nasal endoscopy Lund-Kennedy score postoperatively was 2.76 ± 1.62 at 6th months. In the study conducted by Smith *et al.,* postoperatively mean of Lund-Kennedy score was 4.5 ± 3.7 with a significant mean change of 3.5 ± 4.5 ($P < 0.01$).[15] In the analysis of subgroups by patient factor, all patients irrespective of subgroup showed significant improvement on endoscopy with the exception of smokers. There was no significant difference between smokers ($n = 10$) and non-smokers in change in endoscopy scores.

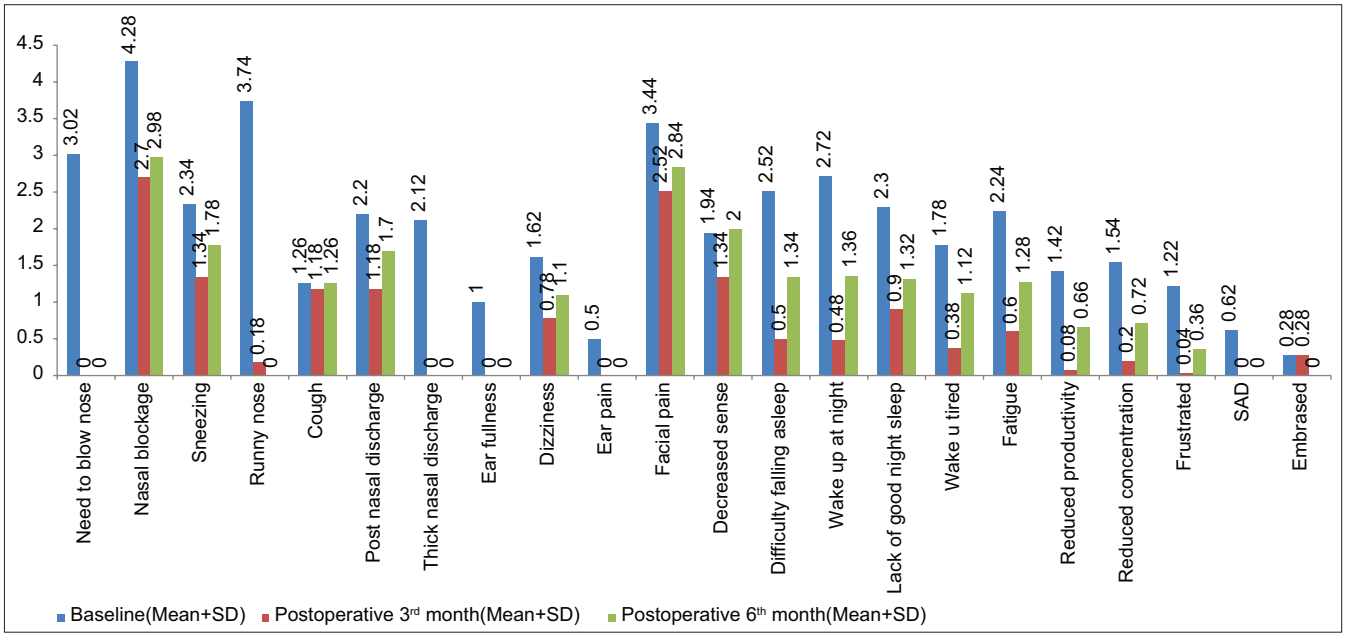

Figure 1: Bar diagram comparing Pre-operative SNOT-22 score with Post-operative SNOT-22 score after 3rd and 6th month of functional endoscopic sinus surgery

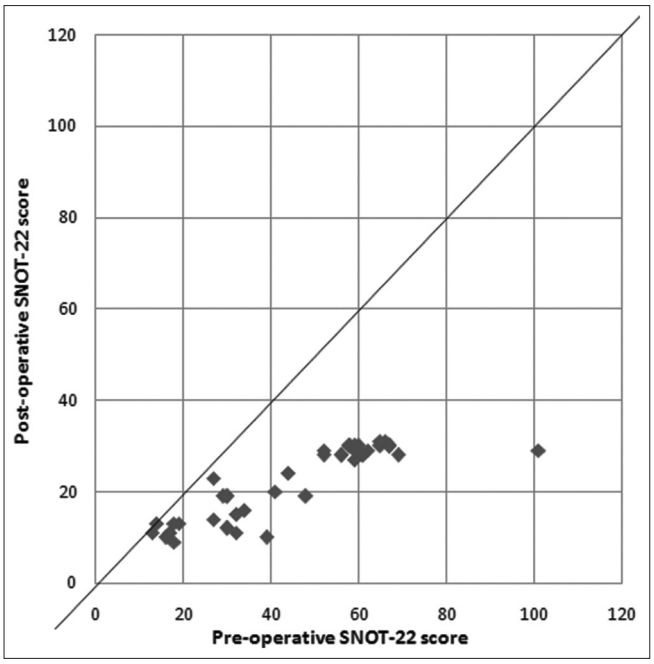

Figure 2: Scatter plot of pre-operative and post-operative SNOT-22 scoring of individual patients

The mean post-operative SNOT-22 score was 14.42 ± 4.78 at 3rd month and 21.82 ± 7.81 at 6th month. There was a statistically significant ($P < 0.01$) decrease in patient reported SNOT-22 scores at 6 months. In Figure 2, scatter plot is shown using individual patients' pre-operative and post-operative (6-month) SNOT-22 mean score. It clearly indicates that all patients were benefitted by the intervention as post-operative symptom score improved in all. Here, we can clearly notice that the patients having higher pre-operative SNOT-22 score have shown greater benefit. Hopkins *et al.* reported mean post-operative SNOT-22 score as 25.5 ± 20.8 at 6 months.[16]

Statistically significant reductions in major and minor symptom scores were achieved for all symptoms. Large effect sizes were noted for reductions in facial pressure, nasal obstruction, congestion, and rhinorrhea. Similar large effect sizes were noted for reductions in headache and fatigue. Moderate effect sizes were noted for hyposmia, fever, halitosis, cough, and ear pain.

CONCLUSION

- SNOT-22 is a self-administered easy to use tool for CRS patients to self-assess improvement in symptom score and it helps in motivation of patient for continuing medical management and nasal irrigation
- Quality of life improves after FESS and nasal steroid irrigation in refractory CRS patients
- Patients with higher pre-operative SNOT-22 score showed relatively better post-interventional SNOT-22 scores.

COMPLIANCE WITH ETHICAL STANDARDS

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Original Article

Role of Abdominal Drains in Perforated Peptic Ulcer Patients: A Prospective, Randomized, and Controlled Study

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Abstract

Introduction: Peptic perforation is the second most complication of peptic ulcer disease. It is a serious condition where an untreated peptic ulcer can perforate through the wall of the stomach [or other areas of gastrointestinal tract]. As the peptic ulcer perforates, it allows the digestive juice to gain entry into the abdominal cavity. The penetrating peptic ulcer was penetrating through the duodenum into the free peritoneal cavity and elicit a chemical peritonitis.

Materials and Methods: This prospective, randomized, and controlled study was done in the Department of General Surgery, IPGME and R and Calcutta National Medical College and Hospital, Kolkata. Patients of peptic perforation (D1 perforation) admitted in surgical indoors within 48 h of onset of symptoms and repaired with Roscoe Graham patch closure. Age: 18–65 years, Sex: both male and female.

Results: Burst abdomen is a very serious complication and a cause of morbidity that is a sequel of wound infection. Burst abdomen was significantly higher in with drain patients 4 (16.0%) than without drain patients 0 (0.0%) and this association was statistical significance (Chi-square value = 4.34, $P = 0.03$). Post-operative nausea and vomiting were associated in two groups of the patients. In Group A, post-operative nausea vomiting was more frequently observed in with drain patients 18 (75.0%) than without drain patients 6 (25.0%) and this association has statistical significance (Chi-square value = 11.54, $P < 0.001$) and we have reached to a result that shows that wound infection including stitch line infection is much higher in Group A patients. High wound infection was found in patients with drain 13 (76.5%), compared without drain group patients 4 (23.5%).

Conclusion: If the proper toileting of the abdominal cavity can be achieved with care, there is no role of putting abdominal drains as prophylactic drainage after Graham's patch repair in cases of perforated peptic ulcer diseases mainly D1 perforation.

Key words: Peptic ulcer, Perforation, Tube drain

INTRODUCTION

Peptic perforation is the second most complication of peptic ulcer disease.[1] It is a serious condition where an untreated peptic ulcer can perforate through the wall of the stomach [or other areas of gastrointestinal tract]. As the peptic ulcer perforates, it allows the digestive juice to gain entry into the abdominal cavity.[2] The penetrating peptic ulcer will penetrate through the duodenum into the free peritoneal cavity and elicit a chemical peritonitis.

Patients of peptic perforation usually present with the upper abdominal pain to start with. Patient can typically recall the exact time of onset of abdominal pain. As time passes, the pain abdomen is accompanied by the onset of fever, vomiting, and respiratory distress. As time progresses, peritonitis starts to build up and patient experiencing pain all over the abdomen. Clinical examination shows tachycardia, low blood pressure, and dehydration. Per abdominal finding reveals an exquisite tenderness over abdomen, absent intestinal peristaltic sounds, card board rigidity of the abdomen, positive rebound tenderness,

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and most importantly obliteration of liver dullness. A hallmark of free perforation is the demonstration of free air underneath the diaphragm on an upright chest radiograph.[3] Many of the perforated ulcers have been attributed to the bacteria *Helicobacter pylori*. The incidence of perforated ulcer is steadily declining, though there is a still incidence where it occurs. Causes include smoking and non-steroidal anti-inflammatory drugs.[4] Peptic perforation mainly D1 perforation the deadly complication of peptic ulcer disease is a surgical emergency. After the diagnosis is made, operation is performed in an expeditious fashion following appropriate fluid resuscitation.[3] Surgery is almost always indicated, although occasionally non-surgical treatment can be used in stable patient without peritonitis if there is sealed perforation.[1] However, in this study, we are only considering non-sealed D1 perforation. The options for surgical treatment of D1 perforation are simple omental Graham's patch repair, patch closure and highly selective vagotomy, patch closure, and vagotomy + Drainage.[1] Here, we are only considering simple Graham's patch repair. There has been an ongoing discussion about the requirement of routine usage of abdominal drains in post-operative cases of simple omental patch repair of D1 perforations. My study seeks to investigate the pros and cons of abdominal drain usage in peptic perforation patients undergoing Graham's patch closure concerning D1 perforation.

Aims

The present practice is to leave two tube drains: One in the Morrison's pouch and one in the pelvis after omental patch closure in cases of perforated peptic ulcer (D1) patients.

This study is going to be conducted to test the efficacy and safety of drain usage routinely after duodenal ulcer perforation (D1 perforation) closure with Roscoe Graham omental patch technique by dividing the whole study into two groups such as Group A and Group B. Group A patients are those who were given abdominal drains intraoperatively in pelvis and Group B patients are those who were not given any drains in the abdomen intraoperatively.

Specific Objective of the Study

The specific objectives of the study are as follows:

1. Compare post-operative morbidity profile between the two groups
2. Comparison of mean hospital stay between the two groups
3. To study the incidence of any intra- abdominal collection in these patients undergoing the study by radiological imaging done on 3rd post-operative day in both groups like ultrasonography (USG)
4. To determine the occurrence of drain site complications
5. To notice the average drain output and nature of drainage fluid in patients given with drain
6. To notice and compare average time for the return of bowel activity in both arms.

MATERIALS AND METHODS

Study Area

The study was conducted at Department of General Surgery, IPGME and R and Calcutta National Medical College and Hospital, Kolkata.

Study Population

Patients admitted in surgical indoors.

Study Period

The study period was 1 ½ years.

Inclusion Criteria

The following criteria were included in the study:

Patients of peptic perforation (D1 perforation) admitted in surgical indoors within 48 h of onset of symptoms and repaired with Roscoe Graham patch closure.

- Age: 18–65 years
- Sex: Both male and female
- Type of surgery: Emergency
- Must be willing to give written informed consent.

Exclusion Criteria

The following criteria were excluded from the study:

- Age out of range [<18 year and >65 year]
- Patient having known bleeding diathesis
- Patients with traumatic gastric/duodenal perforation
- Malignant pathology
- Patients with any other hollow organ perforation
- Patients with chronic liver failure/renal failure/ congestive cardiac failure
- Pregnant women
- Any other clinical condition perceived by the investigator as not conducive to be included in the study.

Study Design

This study was a prospective, randomized, and controlled study.

Sample Size

The sample size was 50 patients.

RESULTS AND DISCUSSION

In this work, we have selected 50 patients, all having peptic perforation (D1 perforation), admitted in the surgical

Table 1: Wound infection and USG whole abdomen to see abdominal and pelvic collection done 3rd post-operative day of the two groups patients

	Group		
	With drain	Without drain	Total
Wound Infection			
No	12	21	33
Row %	36.4	63.6	100.0
Col %	48.0	84.0	66.0
Yes	13	4	17
Row %	76.5	23.5	100.0
Col %	52.0	16.0	34.0
Total	25	25	50
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
USG whole abdomen to see Abdominal and pelvic collection done 3rd post-operative day			
Mild Pelvic, Interloop	5	4	9
Row %	55.6	44.4	100.0
Col %	20.0	16.0	18.0
Mild Pelvic	4	3	7
Row %	57.1	42.9	100.0
Col %	16.0	12.0	14.0
Minimal Pelvic	9	13	22
Row %	40.9	59.1	100.0
Col %	36.0	52.0	44.0
Moderate Pelvic	6	1	7
Row %	85.7	14.3	100.0
Col %	24.0	4.0	14.0
No	1	4	5
Row %	20.0	80.0	100.0
Col %	4.0	16.0	10.0
Total	25	25	50
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0

USG: Ultrasonography

indoor after proper clinical examination such as obliteration of liver dullness, card board rigidity of abdomen, absent IPS, rebound tenderness, and radiological imaging such as demonstration of free air under right dome of diaphragm in straight X-ray abdomen in erect posture/ straight X-ray chest. All these patients were operated after proper resuscitation with iv fluids, iv antibiotics, and catheterization. The early arrival to our hospital may be due to early diagnosis of acute abdomen or the perforation was diagnosed early by the general physician and also the quick availability of the medical services and transport system. We performed Roscoe Graham patch closure of all the 50 cases of D1 perforation followed by thorough peritoneal toileting with normal saline. Thereafter, we placed abdominal drain kit-no 32 in pelvis in Group A patients (those who were given abdominal drains intraoperatively in pelvis) and closed the abdomen without placing drain in the abdominal cavity in Group B patients (those who were not given any drains in the abdomen intraoperatively) as per this study design. We thoroughly followed the post-operative course of both groups of patients. As previously discussed in this study objective, we are considering different parameters to be studied in both groups of patients. Our study wants to establish the pros and cons of abdominal drain, comparing both groups of patients.

We have achieved a result that shows that wound infection including stitch line infection is much higher in Group A patients. High wound infection was found in patients (76.5%) with drain, compared with without drain Group B patients (23.5%). Test of proportion showed that the proportion of with drain group was significantly higher than without drain group (Chi-square value = 5.70; $P < 0.01$). Pessaux *et al.* suggested that drains act as a foreign body and increase the risk of infection. Boey *et al.* showed 36% wound infection rate in their study in Ann 1987 January.[5] Another parameter the result shows that drain site infection in Group A patients is 17 in number and incidence is 68.0%. It is a well-known fact that drain always invites infection and acts as a foreign material at drain site. This high infection rate, like wound infection and drain site infection compel us to rethink and go against the conventional age old approach of putting abdominal drains intraoperatively. In the study shown by Schein in to drain or not to drain? the role of drainage in the contaminated and infected abdomen: An international and personal perspective, World Journal of surgery 2008, 32(2): 312-321,[6] showed that drain site infection is about 10%. In this study, drain site infection is higher than that study. Hence, it is obvious that drain site infection is a well-established morbidity in patients given drains after repair of peptic perforation. Paul *et al.* in their study, prophylactic abdominal drains, got bacterial growths from cultures of the interior portion of their drains, on removal, revealed that in 17 out of 50 of these patients, there were definite skin contaminants on the interior part of their drains. These findings strongly suggest that bacteria do migrate through the drain into the interior. The authors seriously question the routine placement of prophylactic abdominal drains, in view of the increased virulence reported even among commensal microorganisms which migrate down these drains.[7]

Looking into another parameter, such as post-operative fever, here also results is in favor of non-drain group (Group-B). In Group A, post-operative fever was more frequently observed in with drain patients: 22 (73.3%) than without drain patients 8 (26.7%) in Group B and this finding was statistically significant (Chi-square value = 14.08. $P < 0.001$). Higher incidence of fever in Group A was due to high incidence of wound infection and drain site infection in this Group. Pai *et al.*[8] in their study showed that post-operative fever was significantly lower in the non-drain group as compared to drain group. The result of this study corroborates with those studies.

Burst abdomen, sequel of wound infection, is a very serious complication and morbidity to the patients. Burst abdomen was significantly higher in drain group patients numbering 4 patients (16.0%), than without drain group patients 0 (0.0%) and this finding was statistically significant (Chi-square value = 4.34 $P = 0.03$). The age of the patients experiencing burst abdomen is 46 years, 48 years, 60 years, and 40 years. It shows that the prevalence of burst abdomen is higher in older age group. Waquar *et al.* in their study shows that risk of wound dehiscence and burst abdomen increases with advancing age. They showed incidence of wound dehiscence was 57% above age 50.[9] The incidence of several other parameters, the signature of post-operative morbidity, like post-operative nausea vomiting, post-operative abdominal distension, post-operative abdominal pain, and drain site pain, all are higher in Group A patients.

Post-operative nausea vomiting was associated with two groups of the patients. In Group A, post-operative nausea vomiting was more frequently observed in with drain 18 patients (75.0) than without drain 6 patients (25.0%) and this association was statistically significant (Chi-square value = 11. 54, $P < 0.001$). The previous studies by Ansari *et al.* and Petrowsky *et al.* showed increased incidence of nausea and vomiting in patients of drain group in respect to non-drain group. Prolonged immobilization, prolonged antibiotic course to combat wound infection, and drain site infection are the causative factor more incidence of nausea and vomiting in drain group (Group A) patients in this study.

Post-operative abdominal distension was statistically higher in with drain group patients 14 (56.0%) than without drain group patients 4 (16.0%) and this association was statistically significant (Chi-square value = 7.03, $P = 0.008$). Ansari *et al.* found that there was no significant difference between the no drain and drain groups with respect to the post-operative abdominal distension, Pai *et al.* showed mild difference in respect to postoperative abdominal distension between the non-drain and drain group patients. This study shows different results from them. Increased time for the return of bowel activity, and prolonged immobilization, increased infection rate, and all seem to be the risk factor for the increased incidence of postoperative abdominal distension in Group A patients.

Post-operative abdominal pain was statistically higher in with drain patients number that is 23 patients (92.0%) than without drain patients number is 13 patients (52.0%) and this finding was statistically significant (Chi-Square value = 8.03, p= 0.004). All the previous studies by Ansari *et al.*, Petrowsky *et al.*, and Pai *et al.* showed significant difference between with drain and non-drain group in respect to post-operative abdominal distension. This study corroborates with their study. Extra wound for drain, drain site infection, wound infection, wound dehiscence, and all are the causative factor for the high incidence of post-operative abdominal pain in with drain group (Group-A).

Drain site pain is also a parameter in the study. It is also a known parameter of post-operative morbidity. It is only observed in Group A patients. Out of 25 patients, 22 patients experienced pain in the drain site postoperatively. This value is very high and this increased the morbidity to these patients. The incidence is 88% in this Group. Rathi *et al.* in their study entitled "Laparoscopic Cholecystectomy without the use of drain in selected cases" concludes that the use of abdominal drain has been found to be associated with significant drain site pain/discomfort, incidence being 26%.[10] Other studies related to peptic perforation, drain, and non-drain also showed a significant incidence of drain site pain. In this study, the incidence is much higher. Drain site infection also contributes to the high incidence of drain site pain in Group A patients. From the previous literature, it is a well-known fact that maximum patients experience discomfort and pain during removal of all kinds of drain particularly abdominal drains. This study does not differ from this fact. During removal of drains on 5th postoperative day, nearly all patients in Group A experienced discomfort and pain. As the incidence of wound infection, drain site infection, burst abdomen, post-operative fever, drain site discomfort, and pain are much higher in Group A patients naturally average time for duration of hospital stay increases in Group A patients. In Group A, the mean duration of hospital stay (mean ± S.D) of patients was 11.88 ± 1.72 days and in Group B, the mean duration of hospital stay of patients was 7.32 ± 0.69 days. As the mean duration of hospital stay increases in Group A patients, chance of nosocomial infection is high in these group. Many literature proved this previously as, Sheng *et al.* in their study "impact of nosocomial infections on medical costs, hospital stay, and outcome in hospitalized patients" "concluded that nosocomial infections have a significant impact on the length of hospital stay and medical care cost.[11]

Return of bowel activity was compared in both Group pts. In with drain patients, return their bowel activity was 4 (16.0%) in day 2, 18 (72.0%) in day 3, 3 (12.0%) in day 4, but in without drain patient, return their bowel activity was 17 (68.0%) in day 1 and 8 (32.0%) in day 2. Return of intestinal peristaltic sound came early in without drain patients compared to with drain patients and this finding was statistically significant (Chi-square value = 39.33, $P < 0.001$). Pai *et al.* found no significant difference between drain and non-drain group in respect to return of bowel activity in post-operative period.

In Group A, the mean average drain output per day (mean ± S.D.) of patients was 33.46 ± 15.97 ml/day with range 10–70 ml/day and the median average drain output per day was 34 ml/day. Mean drain output <25 ml/day observed in 12 patients, and mean drain output between 25 ml/day and 50 ml/day observed in 11 patients, and mean drain output >50 ml/day observed in two patients. The nature of the content being mostly serosanguinous and sangiunous. There is no evidence of bile, pus, intestinal content in the drainage bag, indicating no post-operative leak, and major intra-abdominal collection of pus. The amount of drain output is negligible in 23 patients. In addition, drains should be removed once the drainage has stopped or becomes <25 ml/day. This can be applied in majority of patients of Group A. Memon *et al.* suggested that "Drains are not substitute for good surgical technique."[12]

Abdominal and pelvic collection evaluated in both group of patients. In Group A patients, USG whole abdomen to see abdominal and pelvic collection, done on 3rd post-operative day, 5 (20.0%) patients showed mild 4 (16.0%) patients showed mild pelvic, 9 (36.0%) patients showed minimal pelvic, 6 (24.0%)patients showed moderate pelvic, and 1 (4.0%) patients showed no collection. In Group B patients, 4 (16.0%) patients showed mild pelvic and interloop collection, 3 (12.0%) patients showed mild pelvic, 13 (52.0%) patients showed minimal pelvic, 1 (4.0%) patients showed moderate pelvic, and 4 (16.0%) patients showed no collection, and this association was not statistically significant (Chi-square value = 6.35, $P = 0.17$). It is clear from the above discussion that both drain and non-drain group developed post-operative abdominal and pelvic collection. Pai *et al.* concluded that routine use of drains was not effective in preventing post-operative fluid collection nor in decreasing the incidence of intra-abdominal abscesses.[8] Per rectal examination to see pelvic collection was observed in drain group (Group A), incidence being 24%, and in without drain group, it is 32%. It can be concluded from this result that one of the main functions of abdominal drains to drain the abdominal and pelvic collection gone in darkness. Two patients out of 25 in Group A, that is with drain group, died. Age of these patients is 46 years and 48 years. Those two patients also experienced burst abdomen and mild-to-moderate pelvic and interloop collection on the ultrasonographic evaluation. Probably sepsis contributes to these mortality [Table 1].

CONCLUSION

In this study, drain-related complications are high. Morbidity and mortality profile is higher in drain group patients in comparison to non-drain group. It is very obvious from this study that putting abdominal drains in cases of peptic perforation (D1 perforation) offer no extra advantage in respect to non-drain group, rather it increases the complication rate.

Hence, if the proper toileting of the abdominal cavity can be achieved with care, there is no role of putting abdominal drains as prophylactic drainage, in cases of perforated peptic ulcer diseases mainly D1 perforation.

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Original Article

Institutional Study for Different Treatment Modalities for Bed Sores in Chronic Bed-ridden Patients at Three Different Hospitals in Gujarat

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Abstract

Introduction: Pressure sore develops due to ischemic changes at epidermis. Pressure ulcers develop primarily from pressure and shears are progressive in nature and most frequently found in bedridden, chair bound, or immobile people. They often develop in people who have been hospitalized for a long time generally for a different problem and increase the overall time as well as cost of hospitalization that have detrimental effects on patient's quality of life. Loss of sensation compounds the problem manifold and failure of reactive hyperemia cycle of the pressure prone area remains the most important etiopathology.

Materials and Methods: Pressure ulcers are largely preventable in nature and their management depends on their severity. From January 2021 to January 2022, total 125 individual surgical cases were considered for study from three different institute in Gujarat. The present treatment options include various approaches of cleaning the wound, debridement, optimized dressings, role of antibiotics, and reconstructive surgery.

Results: Bed sore managed by conservative and operative method such as debridement, vacuum assisted closure therapy, flap coverage depending on wound condition, and patient general condition. Majority of cases were managed with debridement and dressing along with regular physiotherapy. Reconstructive flap was considered for larger defect.

Conclusion: The treatment of pressure ulcers requires careful patient education, intensive multidisciplinary optimization, and meticulous wound care. Post-operative complication was studied and wound infection and recurrence are most common. There for early bed sore care is better.

Key words: Decubitus ulcer, Ischial sore, Wound dehiscence

INTRODUCTION

Pressure ulcers are a type of injury that breaks down the skin and underlying tissue when an area of skin is placed under constant pressure for certain period causing tissue ischemia, cessation of nutrition, and oxygen supply to the tissues and eventually tissue necrosis.[1] Constant pressure resulting in "distortion or deformation damage" is probably the most accurate description of a pressure ulcer. The areas that are particularly prone to pressure sores are those that cover the bony areas such as occiput, trochanters, sacrum, malleoli, and heel.[2] Pressure ulcers are especially morbid after spinal cord injury, leading to high rates of hospitalization and longer hospital stays.[3-5] Despite this high expenditure, patients die as a direct result of these preventable wounds.[6] Septicemia, pneumonia, urinary tract infection, congestive heart failure, respiratory failure, and complicated diabetes mellitus are the most common diagnoses in patients with pressure ulcers.[7] These medical comorbidities significantly impact wound healing. Surgical reconstruction can only be considered following wound debridement and stabilization, infection management, and

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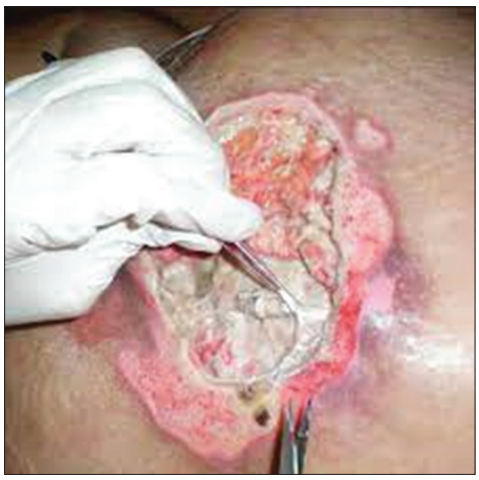
medical and nutritional optimization. Although flap closure is the most commonly recommended reconstruction technique, some surgeons may perform direct closure or skin grafting, these methods are often suboptimal. Unfortunately, failure rates and ulcer recurrences after attempted surgical repair are high.[8] The tissues are capable of sustaining pressure on the arterial side of around 30–32 mm hg for only a small duration of time.[9] However, when pressure increases even slightly above this capillary filling pressure, it causes microcirculatory occlusion and this, in turn, initiates a downward spiral toward ischemia, tissue death, and ulceration. To put it more simply, any individual, with or without a medical condition, who is incapable of avoiding prolonged periods of an uninterrupted compression, is at a risk of pressure ulcers.[10]

Treatment

Where possible, the treatment of ulcers is planned with an aim to reverse the factors that have originally caused the ulcer. Careful assessment is needed before planning for the treatment. In general the possible causative factor should be removed (pressure, shear, and friction) and the associated general condition should be taken into the control (like treatment of associated comorbid illness and improvement in the nutrition).[11] The affected area requires thorough cleaning and dressing. However, since the full range of motion and active physiotherapy of joints do improve circulation, even non-weight bearing physiotherapy is desirable. Wound healing requires adequate protein, iron, Vitamin C, and zinc. Supplements may be prescribed if they are deficient in the diet.[12]

Cleaning and debridement

Cleaning of the wound and meticulous skin care is the most essential part of the treatment. Besides the conventional surgical debridement other types of debridement like mechanical debridement which includes use of repeated wet to dry dressings to removes slough, enzymatic debridement using enzymes to liquefied dead tissue in the wound, and remove them with the dressings and biological debridement or maggots and larval therapy (in which the larvae eat all the dead tissue and make the wound clean without harming the living tissues) also find a mention in the literature. Sharp surgical debridement using blade or scissors is the most commonly used and most effective method of debridement in able surgical hands.[13]



Cleansing and pressure irrigation

Where dead tissue is removed using high-pressure water jets, there is no evidence available to support any specific and effective cleansing techniques or solution, in particular.[14]

Wound dressings

The dressing used for various stages of wound healing is specialized for every stage; in fact, there is a whole range of dressings available to assist with the different stages of wound healing. These are classified as non-absorbent, absorbent, debriding, self-adhering, and many others. It is vital to determine the most appropriate dressing as it ultimately depends on the site/type of ulcer, for hospital care or domiciliary management, personal preference, and cost to the patient.[15] Contaminated or weeping wounds may require more frequent dressing changes, sometimes every few hours. Heavily contaminated ulcers are treated with negative pressure wound therapy (NPWT).

Specialized dressings and bandages are used to protect and speed up the healing process of the pressure ulcers. These dressings include:

Hydrocolloid dressings

These contain a special gel that encourages the growth of new skin cells in the ulcer and keeps the nearby healthy area of skin dry.

Alginate dressings

These are made from seaweed that contains sodium and calcium known to speed up the healing process. Honey-

impregnated alginate dressings are known to accomplish total wound healing to pressure ulcers.

Nano silver dressings

These use the antibacterial property of silver to clean the ulcer.

Creams and ointments

To prevent further tissue damage and help speed up the healing process, topical preparations such as cream and ointments are frequently used.

Antibiotics

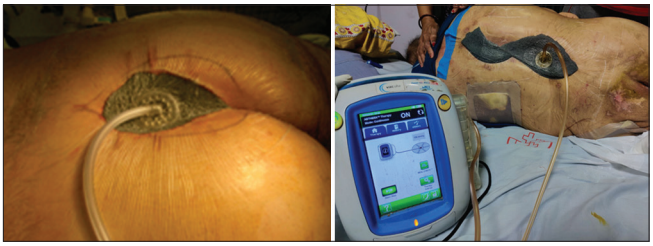
All pressure sores do not require antibiotics. Antibiotics are usually only prescribed to treat an infected pressure ulcer and prevent the infection from spreading. If tissue infection exists, antibiotics are necessary to treat the infection, but effort must be made to debride the ulcer thoroughly and leave all viable tissues only, otherwise antibiotics alone will not clean up the ulcer. Antibiotics are adjunct to surgical debridement and not an alternative to it.

Biofilm

It has been noticed that the longstanding pressure ulcers are frequently colonized by micro-organisms in a biofilm. The biofilm may be composed of bacteria, fungi, or other organisms, which are embedded in and adherent to the underlying wound. We address the problem of biofilm by changing the pH of the wound dressing with dilute ascetic acid if it is alkaline, which it usually is and curetting out all the undermining, cracks and crevices of the ulcer, or by surgical debridement.

NPWT

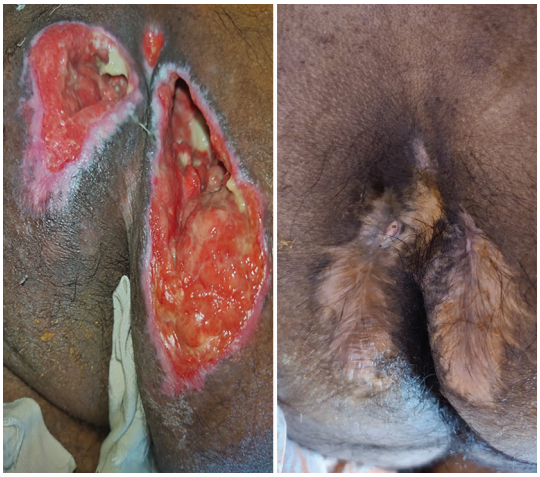
This is an invaluable tool in the management of pressure sores and involves the application of sub-atmospheric pressure to a wound using a computerized unit to intermittently or continuously convey negative pressure to promote wound healing. NPWT is effective for deep, cavitating, infected, and copiously discharging pressure ulcers, particularly with exposed bone.[15] With growing clinical experience, it can be said with certainty that it assists wound healing, and its benefits can be summarized thus:



- Assists granulation
- Applies controlled and localized negative pressure to help uniformly draw wounds closed
- Helps remove interstitial fluid allowing tissue decompression
- Helps remove infectious materials and quantifies exudates loss
- Provides a closed and moist wound healing environment
- Promotes flap and graft survival
- Both hospital and domiciliary use
- Reduces hospital/dressings/nursing cost (if we can discharge the patient to home).

Reconstructive Surgery

Sometimes the severe pressure ulcer (Grade III or IV) fail to heal, in such cases, surgery is required to fill the wound and prevent any further tissue damage. This is usually done by cleaning the wound and closing it by bringing together the edges of the wound (direct closure), application of various type skin grafts, or using local and regional flaps and free tissue transfer.[16]



There are many risks and complications that can occur after surgery, including infection, necrosis of flap, muscle weakness, blisters, recurrence of the pressure ulcers, septicemia, infection of the bone (osteomyelitis), bleeding, abscesses, and deep vein thrombosis. Despite the risks, surgery is often a necessity and the only option to prevent limb and life-threatening complications.[17]

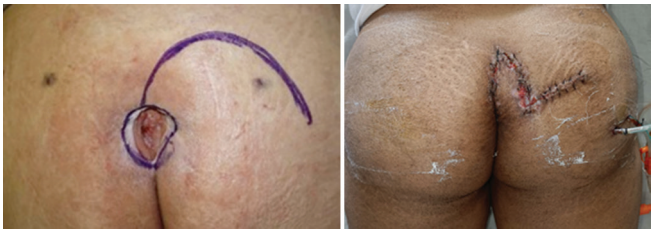
The available reconstructive options are.

Split thickness skin grafting

When the ulcer is superficial and vital tissues such as bone, vessels, nerves, or tendons are not exposed, and the ulcer is not copiously discharging, skin grafting is the first option for surgical treatment. The slimy layer over the surface of ulcer is sharply debrided to get a healthy vascular bed for skin grafting.

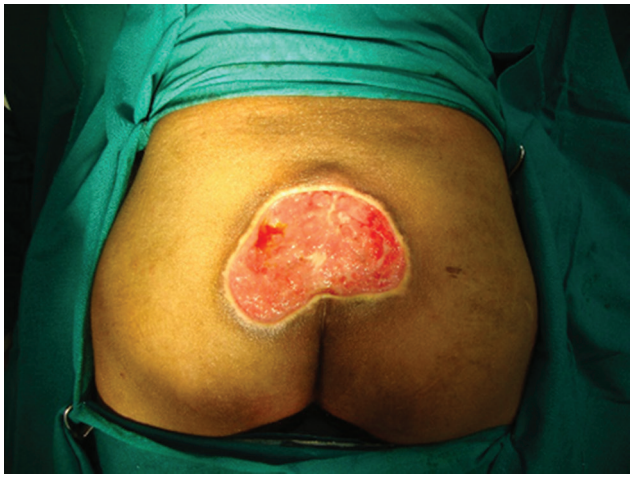
Local flaps

Variety of local flaps can be used to reconstruct the defect created by excision of pressure ulcers. Local transposition, rotation, and limberg flap are the available options. Biceps femoris V-Y advancement (in paraplegics only) for ischial pressure sore and perforator based V-Y advancement is another good options if the anatomy permits.

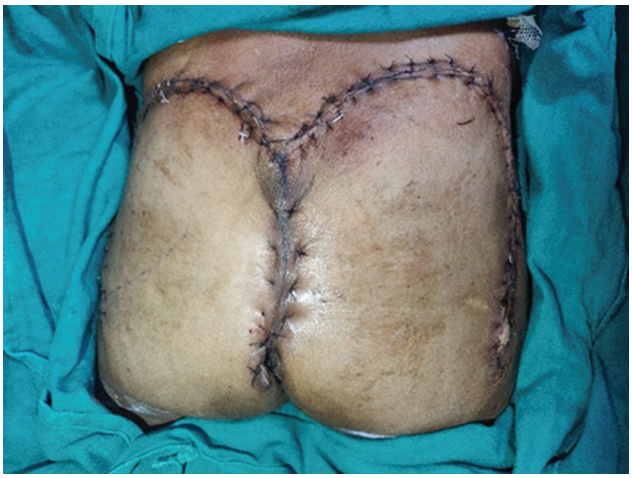


Regional flaps

Sometimes the local or limberg flap cannot close the larger defects due to their size or location resulting in need for regional flaps. For Sacral pressure sores, there are many flap options such as gluteus maximus myocutaneous flap, superior gluteal artery based rotation fasciocutaneous flap, superior gluteal artery perforator flaps, perforator based V-Y advancement flap, and lumbogluteal sensory flap. For lower extremity pressure ulcer reconstruction; Islanded medial planter flap, lateral or medial calcaneal flaps, reverse sural flap, and varieties of fasciocutaneous flaps may provide a huge reconstructive option.



Microvascular free flaps



Microvascular free flaps are usually reserved for some selected cases where the local and regional flap options are either not available or have failed, and the depth of the pressure ulcer demands adequate volume restoration for proper weight bearing. In fact, the latter reason is so vital that many large pressure ulcers on weight bearing soles or on tip of amputation, stumps are today being primarily treated with microvascular free tissue transfer.

Prevention: Mattresses and cushions

Protection is the best way to prevent ulcers. Patients who are at risk of developing pressure ulcers should have the skin carefully inspected for any damage or redness (particularly over bony areas) twice daily. The skin should be kept clean and dry. Any pressure causing damage to skin or tissue should be immediately eliminated. This can be done with the help of special mattresses, cushions, and by many protective devices that can relieve the external pressure on vulnerable areas of body limbs.[18] For small areas like hand, ankle, and foot, we use water filled tied surgical hand gloves as pressure relieving devices at hospital setup and we advise the patients to use these at their home as a very easy to make and very low-cost pressure relieving device.[19]

Pressure ulcers put a greater health risk to regular users of wheelchairs or those who are bound for prolonged sitting. The most frequently involved areas while seating are sacrum, coccyx, ischial tuberosities, and greater trochanters. Further, patients or their caretakers are taught to conduct pressure release movements or weight shifts

on regular intervals to prevent pressure concentration and tissue damage. Patients who sit for a long time need to use protective cushioning/fabricated air mattresses for protection of bony points and do periodic change of postures and offloading of pressure points by side bending, forward bending, and lifting off the chair with powerful upper body muscles.[20-22]

MATERIALS AND METHODS

This retrospective study was carried out at B. J. Medical College, Ahmedabad. Government Medical College, Surat, and M. K. Shah Medical College and Research Center, Ahmedabad. Inclusion criteria were adult patients of any age and sex with sacral, ischial, and trochanteric pressure ulcers that required of surgical intervention between January 2021 and January 2022. Patients with pressure ulcers managed conservatively or that required wound debridement and/or primary closure without flap coverage were also included in the study. Further exclusion criteria were patient with general condition poor and not willing to participate in study. Database that collects variables for each surgical procedure including pre-operative risk factors, intra-operative variables, and 30-day post-operative mortality and morbidity outcomes.

Patient data collected included age, sex, body mass index (BMI), race, medical comorbidities, surgical history, medications, American Society of Anesthesiologists physical status classification system, and tobacco use. Pressure ulcer characteristics including wound location, size, and presence of osteomyelitis (acute or chronic) were also recorded. Operative details recorded included donor site, flap composition, and procedure length. Post-operative management and outcomes collected included length of follow-up and complications including recurrence, wound dehiscence, and infection. The primary outcomes for our review were major complications, which included ulcer recurrence, wound dehiscence, post-operative infection, flap necrosis, and minor complications such as seroma and hematoma.

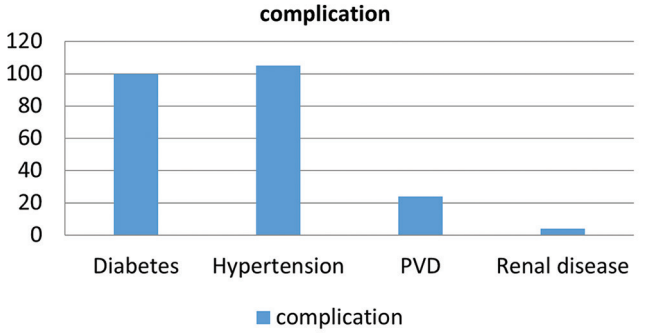
RESULTS

From January 2021 to January 2022, total 125 individual surgical cases were retrieved from the database and reviewed. Total cohort demographic information is listed below. The mean age at time of surgery was 52 years (±17.12) and the majority of patients were male (64%). Ninety-six patients underwent flap coverage of their pressure ulcers. Following is patient demographic and wound characteristics. The average BMI was 24.1 and 40.3% of patients were active smokers. Paralysis was noted in 85.6% of chronic bed-ridden patients, with 16% having quadriplegia and 72% having paraplegia. Of note, 28% of patients had ischial pressure ulcer.

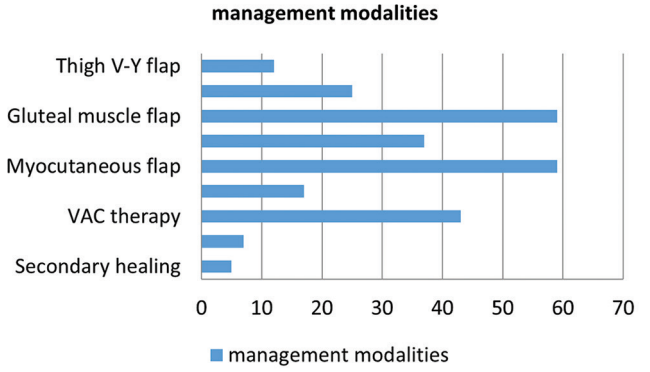
Demographic data		
Male	80	64%
Female	45	36%
Total	125	Mean age 52 year

Paralysis data		
Paraplegia	90	72%
Quadriplegia	20	16%

Type of ulcer		
Ischial	35	28%
Sacral	65	52%
Trochanteric	20	16%
other	05	04%

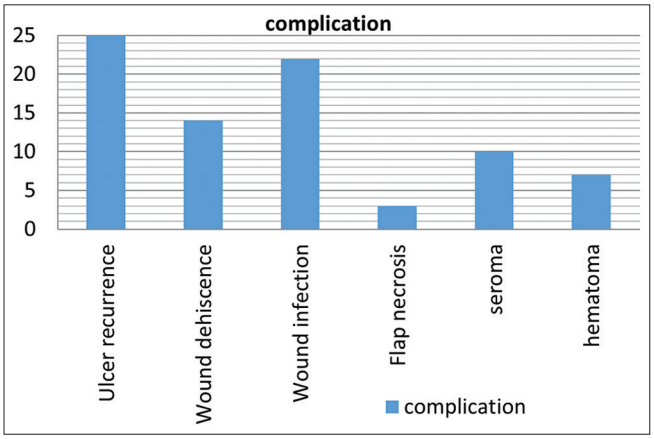


Management modalities		
Secondary healing	5	4%
Primary closure of wound	7	5.6%
Vacuum assisted closure therapy	43	34.4%
STG	17	13.6%
Myocutaneous flap	59	47.2%
Fasciocutaneous flap	37	29.6%
Gluteal muscle flap	59	47.2%
TFL flap	25	20%
Thigh V-Y flap	12	9.6%



The most commonly performed flap utilized the gluteal muscle flap (47.2%). The majority of reconstructive flaps

Complication		
Ulcer recurrence	25	20%
Wound dehiscence	14	11.2%
Wound infection	22	17.6%
Flap necrosis	3	2.4%
seroma	10	8%
hematoma	7	5.6%



were myocutaneously based (47.2%). Complications including major ones (ulcer recurrence, wound dehiscence, post-operative infection, and flap necrosis) and minor ones (seroma and hematoma) occurred in 81 (64.8%) patients in this series. The average albumin was significantly lower in those with complications. Age, sex, race, BMI, diabetes, smoking status, pre-operative osteomyelitis, and flap choice were not risk factors for complications.

DISCUSSION

Pressure ulcers continue to be a medical and economic burden. They represent a significant source of infection and can lead to complications including sepsis, osteomyelitis, immobility, and death. Despite widespread prevention campaigns, it is unclear which measures are cost-effective and there has been little change in the reported incidence of pressure ulcers over time. While some ulcers can be treated with conservative measures, many will go on to receive surgical reconstruction. Post-operative complications further raise the already substantial cost of surgery. Total dependency was associated with a decreased rate of surgical site infection. In this patient population, dependency on nursing staff for local wound care may account for this observation of decreased surgical site infection The rate of wound dehiscence following pressure ulcer reconstruction is variable in the literature and difficult to quantify.

Ischial pressure ulcers were an independent risk factor for pressure ulcer recurrence and wound dehiscence. This finding is not surprising given that ischial tuberosities have increased pressure over other bony prominences in the sitting position. The previous reviews have also found that ischial pressure ulcers are at risk for recurrence. Unfortunately, ischial pressure ulcers are the most common pressure ulcer, and avoidance of flap coverage for ischial pressure ulcers is not an ethical option. Rather, reducing other patient risk factors for flap complications may be important in those with ischial pressure ulcers.

Smoking was an independent risk factor for pressure ulcer recurrence in our retrospective series. Smoking has not been previously linked to pressure ulcer flap complications, so this appears to be a novel finding. Smoking is a risk factor in wound complications in the general plastic surgery population and especially those undergoing free flaps because smoking is a modifiable risk factor, motivational coaching directed toward smoking cessation may be an important step in preventing recurrence. Our data indicate that surgeons should be cautious about offering pressure ulcer flap coverage in smokers and patients should be counseled on the risks associated with smoking.

Nutritional factors are considered to play a role in the development and recovery from a pressure ulcer. Specifically, low prealbumin and albumin levels have been implicated in the development of pressure ulcers. Our review revealed that low albumin and prealbumin were associated with complications. Low albumin was specifically associated with wound dehiscence. However, albumin and prealbumin have inversely correlated with morbidity and mortality across surgical disciplines. Because these are imperfect markers, serum levels of albumin and prealbumin should be considered in light of other clinical findings when making the decision to offer elective flap coverage for a pressure ulcer.

Underlying osteomyelitis can be challenging to diagnose in patients with pressure ulcers and is likely underdiagnosed. In our study, acute osteomyelitis was an independent risk factor for wound dehiscence. Curiously, those with chronic osteomyelitis were not at increased risk for wound complications nor was there an increased risk of infection or ulcer recurrence noted in those patients with active osteomyelitis. Given these findings, it is appropriate to delay pressure ulcer reconstruction in those with active infections to avoid wound complications.

CONCLUSION

The treatment of pressure ulcers requires careful patient education, intensive multidisciplinary optimization, and meticulous wound care. The complication rate following

pressure ulcer repair is high. Careful patient selection and flap-based reconstruction may mitigate these risks.

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Original Article

Comparison of Short-term Results of Laparoscopic (Transabdominal Preperitoneal) Versus Kugel Mesh Repair of Inguinal Hernia

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Abstract

Introduction: There has been an evolution in the treatment of inguinal hernia. While the transabdominal preperitoneal (TAPP) laparoscopic hernia repair is associated with reduced post-operative pain and faster recovery, the Kugel mesh repair offers the advantages of preperitoneal inguinal hernia repair without the need of general anesthesia, combining the advantages of the open technique and the laparoscopic repair of inguinal hernia.

Materials and Methods: The study was carried out in the Department of General Surgery of The Calcutta Medical Research Institute, Kolkata. A total of 50 patients for each procedure were recruited for the study. This study included patients above the age of 18 years requiring surgery for unilateral inguinal hernia who attended the outpatient department of Dr. Sanjay De Bakshi and Dr. Ajay Mandal in The Calcutta Medical Research Institute, Kolkata.

Results: Post-operative pain at 24 h and at 48 h of the patients who had undergone Kugel mesh repair was significantly higher than those of the patients with laparoscopic (TAPP) repair (post-operative pain – at 24 h: $P < 0.0001$ and at 48 h: $P < 0.001$). However, there was no significant difference in the post-operative pain at 7 days for the patients of the two groups ($P = 0.38$).

Conclusion: Short-term results of laparoscopic (TAPP) repair of inguinal hernia were better when compared to the Kugel mesh repair of inguinal hernia. Studies with longer follow-up are recommended so that the recurrences can be analyzed correctly. We recommend randomized and controlled trials with a larger sample size and compared over a longer period of time to draw any strong conclusions.

Key words: Hernia, Laparoscopy, Tissue

INTRODUCTION

Hernia is defined as an abnormal protrusion of an organ or tissue through a defect in the surrounding walls. Inguinal hernias constitute 75% of all hernias.[1]

The first true anatomical repair of inguinal hernia was described by Bassini (1844–1924).[2] There has been an evolution in the treatment of inguinal hernia since then due to the technological advances made in this field. One of the advancement includes the use of mesh. Open tension free hernia repair is superior to conventional pure tissue repair due to less pain, lesser recurrence, and rapid return to normal activities.

Laparoscopic hernia repair was first introduced by Ger[3] in 1981. Corbit[4] and Arregui *et al.*[5] introduced transabdominal preperitoneal (TAPP) laparoscopic hernia repair. A further development of the TAPP hernia repair was the establishment of the total extraperitoneal (TEP) laparoscopic hernia repair by Dulucq in Europe in the early 1990s.[6]

Laparoscopic hernia repair is associated with reduced post-operative pain and faster recovery when compared to conventional anterior repair but is costly, requires high technical skills and longer operative time.

In 1999, Dr. Kugel introduced Kugel repair of inguinal hernia. It was a non-laparoscopic preperitoneal technique.[7]

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In the classic Kugel groin hernia repair, the placement of the mesh in the preperitoneal space was through posterior approach. Thus, it had a steeper learning curve than the traditional anterior approach since entering of the preperitoneal space was through an anatomy quite different from the conventional open hernia methods. To minimize this learning curve, Modified Kugel (Bard-Davol Inc., RI, USA) repair was developed in which the mesh was placed in the preperitoneal space through the anterior approach.

The Kugel mesh repair of inguinal hernia has been found to be as safe as the Lichtenstein hernia repair with similar complication rates.[8-10] Further, it offers the advantages of preperitoneal inguinal hernia repair without the need for general anesthesia thus increasing patient comfort postoperatively. It also does not require specialized instruments thus decreasing the cost considerably. This open technique of Kugel mesh repair aims to combine the advantages of the open technique and the laparoscopic repair of inguinal hernia.

However, recent studies differ in their reporting of superiority among these two procedures. While a prospective study[11] favored Kugel repair over TEP laparoscopic repair, a retrospective study[12] favored laparoscopic (TAPP/TEP) repair over modified Kugel repair.

Till date, there have been inadequate studies comparing the TAPP laparoscopic repair with the Kugel mesh repair of inguinal hernia. This study focuses on the short-term results of TAPP laparoscopic repair and the Kugel mesh repair of inguinal hernia thus further helping in the better understanding of these two procedures.

Aims and Objectives

Aim

The aim of the study was comparison of short-term results of laparoscopic (TAPP) versus Kugel mesh repair of inguinal hernia.

Objectives

To study and compare laparoscopic (TAPP) and Kugel mesh repair of inguinal hernia with respect to the following parameters:

1. Post-operative pain at 24 h, 48 h and at 7 days by numeric pain rating scale.
2. Resumption of routine activities at 24 h and at 48 h postoperatively by:

i. Mobilization out of bed:
   - With assistance
   - Without assistance.

ii. Ability to reach toilet
   - With assistance
   - Without assistance.

3. Length of post-operative stay in hospital in days
4. Failure rates as measured by recurrences at 6 months

MATERIALS AND METHODS

Study Site

The study was carried out in the Department of General Surgery of The Calcutta Medical Research Institute, Kolkata.

Study Population

This study included patients above the age of 18 years requiring surgery for unilateral inguinal hernia who attended the outpatient department of Dr. Sanjay De Bakshi and Dr. Ajay Mandal in The Calcutta Medical Research Institute, Kolkata.

Study Design

This was a prospective, observational, and comparative study.

Sample Size

Formula for computing sample size to compare two groups:
Mean of group 1= M1
Mean of group 2= M2
Common standard deviation (SD) =σ
Effect Size = Difference per SD(DSD) = (M1-M2)/σ
(Absolute difference of M1 and M2 is used for calculation).

As per the study by Li *et al.*,[13] the mean duration of post-operative stay in hospital of the patients of modified Kugel group and laparoscopic (TEP/TAPP) group was 4.03 ± 2.49 days and 1.83 ± 1.59 days, respectively, (n1 = 530 and n2 = 1230).

Here, M1 = 4.03, M2 = 1.83, and Common SD = 2.05. Thus, the effect size = 1.07. From the Cohen Power Tables for effect size, it had been found that there was a need of 50 patients per group with 99% power at 2% level of significance. The number of patients in each group was in the ratio 1:1. Thus, the required sample size for the study was 100.

Study Duration

This study was conducted over a period of 1 ½ years from July 2016 to December 2017 in the Department of General Surgery of The Calcutta Medical Research Institute, Kolkata.

Inclusion Criteria

The following criteria were included in the study:

1. Consecutive patients of Dr. Sanjay De Bakshi for Kugel mesh repair and of Dr. Ajay Mandal for TAPP laparoscopic repair of inguinal hernia
2. Patients above the age of 18 years.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients who underwent another concomitant procedure
2. Patients with bilateral inguinal hernia
3. Patients with recurrent inguinal hernias
4. Patients with irreducible inguinal hernia
5. Patients with obstructed inguinal hernia
6. Patients with strangulated inguinal hernias
7. Patients with cardiac disease
8. Patients with respiratory distress
9. Patients with bladder outlet obstruction
10. Patients who had any orthopedic deformity that precluded ambulation
11. Patients who had any psychiatric illness.

Data Collection Technique and Tools

A detailed history of the patient, clinical examination, and post-operative pain at 24 h, 48 h, and at 7 days by numeric rating scale (which was enquired over the phone) was collected. Resumption of routine activities as measured by mobilization out of bed and the ability to reach the toilet with or without assistance at 24 h and at 48 h postoperatively was collected. Post-operative stay in hospital in days and failure rate as measured by recurrences at 6 months was collected. All data were noted in the study proforma (given in the appendix) and tabulated in Microsoft Excel.

Statistical Methods

Statistical analysis was performed with help of Epi Info (TM) 7.2.2.2. EPI INFO is a trademark of the Centers for Disease Control and Prevention.

Using this software, basic cross-tabulation, inferences, and associations were performed. Chi-square test was used to test the association between different variables under study. Fisher exact test was used in case of Chi-square test being not applicable. Z-test (Standard Normal Deviate) was used to test the significant difference between two proportions. *t*-test was used to compare the means. Odds ratio was calculated with 95% confidence interval to find different risk factors. One-way analysis of variance followed by Tukeys test with critical difference was used to compare the means of more than two groups.

$P < 0.05$ was considered statistically significant.

Ethical Issue

The study obtained the necessary clearance from the Scientific and Ethical Committee of the institute before data collection (attached in appendix).

RESULTS

The aim of this study was to compare the post-operative pain, resumption of routine activities, length of post-operative stay and recurrence for laparoscopic (TAPP), and Kugel mesh repair of inguinal hernia.

We observed that the post-operative pain at 24 h and at 48 h of the patients who had undergone Kugel mesh repair was significantly higher than those of the patients with laparoscopic (TAPP) repair (post-operative pain – at 24 h: $P < 0.0001$ and at 48 h: $P < 0.001$). However, there was no significant difference in the post-operative pain at 7 days for the patients of the two groups ($P = 0.38$).

Resumption of routine activities at 24 h and at 48 h postoperatively was noted. The need for assistance for mobilization out of bed at 24 h among the patients with Kugel mesh repair was 4.17 times more as compared to the patients with laparoscopic (TAPP) hernia repair ($P < 0.0001$). The need for assistance to reach toilet at 24 h among the patients with Kugel mesh repair was also 4.17 times more as compared to the patients with laparoscopic (TAPP) hernia repair ($P < 0.0001$). However, all the patients of the two groups were able to mobilize out of bed and were able to reach toilet at 48 h without any assistance.

It was observed that the post-operative hospital stay of the patients with Kugel mesh repair was significantly higher than that of the patients with laparoscopic (TAPP) repair ($P < 0.0001$).

There was no failure at 6 months for all the patients of the two groups.

There was no significant difference noted among the two groups when compared in terms of distribution of mean age ($P > 0.05$) and sex or diagnosis ($P > 0.05$) of the patients of the two groups [Table 1].

DISCUSSION

Inguinal hernias include direct, indirect, and femoral hernias. All these account for approximately 75% of abdominal wall hernias.[14] The lifetime risk of inguinal hernia is 27% in men and 3% in females.[15]

Inguinal hernia repair underwent transformation with the advent of minimally invasive surgery. Laparoscopic inguinal hernia repair (TAPP/TEP) minimizes post-operative pain and improves recovery.

Table 1: Distribution of diagnosis of the patients, post-operative pain at 24 h of the patients, post-operative pain at 48 h of the patients, post-operative pain at 7 day of the patients, mobilization out of bed at 24 h of the patients, ability to reach toilet at 24 h of the patients, and duration of hospital stay of the patients with two groups

	Kugel mesh repair (*n*=50)	Laparoscopic (TAPP) (*n*=50)	Total
Diagnosis			
Left direct	7	14	21
Row %	33.3	66.7	100.0
Col %	14.0	28.0	21.0
Left Indirect	16	11	27
Row %	59.3	40.7	100.0
Col %	32.0	22.0	27.0
Right Direct	14	9	23
Row %	60.9	39.1	100.0
Col %	28.0	18.0	23.0
Right Indirect	13	16	29
Row %	44.8	55.2	100.0
Col %	26.0	32.0	29.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Post-operative pain at 24 h			
1 – 4	17	41	58
Row %	29.3	70.7	100.0
Col %	34.0	82.0	58.0
5–8	33	9	42
Row %	78.6	21.4	100.0
Col %	66.0	18.0	42.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±s.d.	5.30±1.58	3.16±1.30	t_{98}=7.39
Median	5.00	3.00	*P*<0.0001
Range	3–8	1–6	
Post-operative pain at 48 h			
0–4	41	50	91
Row %	45.1	54.9	100.0
Col %	82.0	100.0	91.0
5–8	9	0	9
Row %	100.0	0.0	100.0
Col %	18.0	0.0	9.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±s.d.	3.00±1.56	1.74±1.19	t_{98}=4.52
Median	3.00	1.50	*P*<0.001
Range	1–8	0–4	
Post-operative pain at 7 day			
0–2	48	50	98
Row %	49.0	51.0	100.0
Col %	96.0	100.0	98.0
3–5	2	0	2
Row %	100.0	0.0	100.0
Col %	4.0	0.0	2.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±s.d.	0.98±0.94	0.22±0.42	t_{98}=1.23
Median	1.00	0.00	*P*=0.38
Range	0–5	0–1	
Mobilization out of bed at 24 h			
With assistance	23	1	24
Row %	95.8	4.2	100.0
Col %	46.0	2.0	24.0
Without assistance	27	49	76
Row %	35.5	64.5	100.0
Col %	54.0	98.0	76.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Ability to reach toilet at 24 h			
With assistance	23	1	24
Row %	95.8	4.2	100.0
Col %	46.0	2.0	24.0
Without assistance	27	49	76
Row %	35.5	64.5	100.0
Col %	54.0	98.0	76.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Duration of hospital stay (in days)			
1	0	40	40
Row %	0.0	100.0	100.0
Col %	0.0	80.0	40.0
2	38	10	48
Row %	79.2	20.8	100.0
Col %	76.0	20.0	48.0
3	12	0	12
Row %	100.0	0.0	100.0
Col %	24.0	0.0	12.0
Total	50	50	100
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±s.d.	2.24±0.43	1.20±0.40	t_{98}=12.44
Median	2.00	1.00	*P*<0.0001
Range	2–3	1–2	

The Kugel mesh repair of inguinal hernia is known to strengthen all three defect areas of the myopectineal orifice simultaneously. Besides, the Kugel patch is fixed by intra-abdominal pressure making the procedure sutureless, thus avoiding injuries to nerves and vessels. Even the preperitoneal space that the Kugel patch is inserted into, is a deep space that is devoid of nerves or vessels which results in the post-operative pain and the foreign body sensation to be less.

A number of studies have been conducted with the modified Kugel technique of inguinal hernia repair.

In the study conducted by Reddy *et al.*[16] wherein 107 inguinal hernia repairs were analyzed, the visual analog pain scores ranged from 0 in 19 patients to a score of 10 in one patient reported on the first post-operative day. However, in similar studies, mild pain was reported which disappeared within 2–3 days of surgery.

Twelve of the 66 patients in the study conducted by Reddy *et al.*[16] who previously had unrestricted walking ability

noted restriction on post-operative day 7. However, Li *et al.*[17] in his study noted ambulation only 6 h after surgery.

The previous studies noted the mean post-operative hospital stay to be 4 days while recurrences were noted to be ranging from 0 to 4 over a period of 2 years.

The only study wherein comparative assessment was done between the laparoscopic (TAPP/TEP) (n = 1230: TAPP-451, TEP-779) repair and the modified Kugel repair (n = 530) was reported by Li *et al.*[12] The visual analog score expressed as mean ± SD was found to be 2.37 ± 1.1 for the modified Kugel repair group and 2.21 ± 0.98 for the laparoscopic (TAPP/TEP) repair group at 24 h after operation ($P < 0.01$). The duration of post-operative hospital stay expressed as mean ± SD was found to be 4.03 ± 2.49 for the modified Kugel repair group and 1.83 ± 1.59 for the laparoscopic (TAPP/TEP) repair group ($P < 0.001$). In addition, more patients in the laparoscopic group (TAPP/TEP) returned to unrestricted movement at two post-operative weeks than the modified Kugel group ($P < 0.01$). The recurrence rate was found to be 1.19% (n = 6) in the open group and 0.51% (n = 6) in the laparoscopic (TAPP/TEP) group. All the recurrences were noted to occur within 3–35 months after surgery except for two recurrences in the open group which occurred later than 2 years after surgery.

Thus, the laparoscopic (TAPP/TEP) group had lower VAS scores with shorter duration of post-operative stay. Moreover, more patients in the laparoscopic (TAPP/TEP) group returned to unrestricted movements earlier. The recurrence was also noted to be lower in the laparoscopic (TAPP/TEP) group.

In the present study, we found that laparoscopic (TAPP) repair of inguinal hernia is better than Kugel mesh repair of inguinal hernia in terms of post-operative pain, resumption of routine activities, and length of post-operative stay in hospital.

In the present study, the post-operative pain at 24 h and at 48 h for the patients who underwent laparoscopic (TAPP) repair of inguinal hernia was significantly low as compared to the patients who underwent Kugel mesh repair of inguinal hernia (at 24 h: $P < 0.0001$ and at 48 h: $P < 0.001$) which was in concordance with the study conducted by Li *et al.*[12] (at 24 h: $P = 0.006$).

We found that the necessity of assistance for mobilization out of bed and of the ability to reach toilet at 24 h among the patients with Kugel mesh repair was 4.17 times more as compared to the patients of laparoscopic (TAPP) inguinal hernia repair ($P < 0.0001$). In the study of Li *et al.*,[12] return to unrestricted movements at second post-operative week was observed to be better ($P < 0.01$) in the patients who underwent laparoscopic repair of inguinal hernia.

In the present study, the mean post-operative hospital stay of the patients with Kugel mesh repair was significantly higher than that of the patients with laparoscopic (TAPP) repair of inguinal hernia ($P < 0.0001$) which is also in concordance with the study conducted by Li *et al.*,[12] wherein the same was observed ($P < 0.01$).

We did not find any recurrence when patients were followed up for a period of 6 months. In the study conducted by Li *et al.*,[12] the recurrence rate was found to be 1.19% for the Kugel mesh repair of inguinal hernia while it was found to be 0.51% in the laparoscopic repair of inguinal hernia.

This difference in recurrence might be due to the shorter time period of follow-up of the present study. However, in the study of Li *et al.*,[12] all groin hernia patients older than the age of 18 years who underwent Kugel mesh repair or laparoscopic inguinal hernia repair between January 2008 and December 2010 were recruited and thus the ratio of patients who underwent laparoscopic repair was not 1:1, whereas in the present study, the distribution of patients in each group was in the ratio of 1:1, thus resulting in the analysis being comparable. In the present study, single surgeon performed each procedure resulting in the analysis being more accurate.

The present study has certain shortcomings, such as small sample size, small period of follow-up, consideration of intra-operative and post-operative complications, and cost of treatment which we have not compared. Randomized and controlled trials (RCTs) on larger sample size and consideration of all the aspects mentioned above need to be done to establish the superiority of laparoscopic (TAPP) hernia repairs with Kugel mesh repair of inguinal hernia.

CONCLUSION

From the present study, we observed that the short-term results of laparoscopic (TAPP) repair of inguinal hernia were better when compared to the Kugel mesh repair of inguinal hernia in terms of post-operative pain, resumption of routine activities, and duration of post-operative stay in hospital. We, thus, recommend the use of laparoscopic (TAPP) repair for unilateral inguinal hernia in healthy adults.

However, the present study was a prospective study with a small sample size. Studies with a larger sample size are recommended to come to strong conclusions.

We recommend the use of one standardized anesthesia in further studies to allow the analysis to be made more accurately.

Studies with longer follow-up are recommended so that the recurrences can be analyzed correctly.

We recommend RCTs with a larger sample size and compared over a longer period of time to draw any strong conclusions.

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Original Article

Pterygium Excision Bare Sclera Technique versus Autologous Conjunctival Autograft: A Prospective Study

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Abstract

Introduction: Pterygium is a fibrovascular growth encroaching from the conjunctiva into the cornea. This study deals with the comparison of conjunctival autograft and bare sclera technique as treatment options for pterygium.

Materials and Methods: This study was done in the Ophthalmology Department of Government Medical College, Doda, Jammu and Kashmir. A total of 100 patients, diagnosed of pterygium were taken for the study, out of which 60 patients were operated on with conjunctival autograft and 40 patients were operated with bare sclera technique. Patients with hypertension, diabetes mellitus were excluded from the study. Post-operative complications and recurrence were noted. All the patients were between the age group of 20–65 years.

Results: The maximum age was 63 and the minimum age was 23 in conjunctival autograft whereas in bare sclera technique, the maximum age was 64 and the minimum age was 22. The recurrence rate of pterygium in conjunctival autograft was 1 (1.67%) and the recurrence rate of pterygium in bare sclera technique was 6 (15%).

Conclusion: The present study revealed that conjunctival autograft was a better treatment option compared to the bare sclera technique for excision of pterygium.

Key words: Conjunctival autograft, Fibrovascular Growth, Pterygium

INTRODUCTION

Pterygium, a wing-shaped fibrovascular growth of the bulbar conjunctiva, is a common chronic ophthalmic condition.[1,2] Although pterygium is generally regarded as a benign and cosmetic concern, without proper treatment, it may result in significant visual morbidity or even potentially blindness in extreme stages.[3,4] Pterygium is commonly seen in India, which is a part of the pterygium belt.[5] It is a potentially blinding disease in the advanced stage when it encroaches visual axis, which can have significant impact on vision and require surgery for visual rehabilitation.[6] Although the etiology of pterygium is unclear, the most common risk factor is ultraviolet light exposure, which induces oxidative stress and the expression of cytokines and growth factors in pterygial epithelial cells, initiating the cellular proliferation, blood vessel formation, tissue invasion, and inflammation.[7] Meanwhile, other confirmed risk factors include dry, warm, dusty climates; high winds; age; and sex.[8] Several modes of inheritance have also been reported such as autosomal-dominant, autosomal-recessive, sex-linked, and non-Mendelian modes of inheritance.[9]

Surgical techniques which have been commonly used for the excision of pterygium are bare sclera, conjunctival autograft, and amniotic membrane transplantation, but none of it is universally accepted because of variable recurrence rates. Thus, the adjunctive medical therapies have been included into the management of pterygium and they are conjunctival flaps, lamellar keratoplasty, mucous membrane grafts, chemotherapy by Thiotepa, radiation therapy by radon bulbs, radium plaques, beta irradiation ablation with erbium YAG laser, smoothening the corneal

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surface with excimer laser, and antimetabolite such as 5-fluorouracil and Mitomycin C but all these adjunctive medical therapies have their own potential side effects.[10]

The aim of present study was to a comparison between conjunctival autograft with bare sclera technique in pterygium excision and its recurrence.

Aims and Objectives

The aim of te study was to evaluate the efficacy, safety, and recurrence rates of conjunctival autograft and bare sclera techniques in the treatment of pterygium.

MATERIALS AND METHODS

The present study was conducted in the Government Medical College Doda, Jammu and Kashmir, between the period of 2019 and 2021. A total of 100 eyes diagnosed with pterygium, of which 60 eyes (37 males and 23 females) operated with conjunctival autograft technique and 40 eyes (26 males and 14 females) were operated with bare sclera technique selected for the study. All patients, that is, male and female patients in the age group of 20–65 years were included in this study. Both the genders were enrolled in the study. The patients having hypertension, diabetes mellitus, cataracts, dry eye syndrome, and pseudo pterygium were excluded from the study. All the patients were told to fill up the name, age, and sign in the standard consent form after explaining the surgery and the study.

These were all primary patients with Grade I to Grade II pterygium. Pterygium was graded depending on the extent of corneal involvement: Grade I – crossing the limbus, Grade II – mid-way between limbus and pupil, Grade III – reaching up to pupillary margin, and Grade IV – crossing pupillary margin. Surgeries were performed by one surgeon with the same protocols so as to avoid any surgical bias.

Pre-operative Procedures

Routine investigations such as blood pressure complete blood count, blood sugar test, and detailed slit lamp examination were done before the operation.

Operative Procedure

In case of bare sclera technique, only topical anesthesia (Proparcaine eye drop) was used. Barraquer wire speculum was used to open and hold the lids. Body of pterygium is dissected about 4 mm from limbus, down to bare the sclera and reflected over cornea. The pterygium head is avulsed using Lims forceps and crescent blade. Remnants over cornea were cleaned with crescent blade. Hemostasis was achieved with bud. Pad and Bandage were done for 24 h. Patient was called next day. Antibiotic steroid eye drops were given for 4 weeks and NSAID on as and when required.

For conjunctival Autograft technique, peribulbar anesthesia is given using Xylocaine 2% with adrenaline. Speculum is used to open the eye. All surgeries were performed under operating microscope. Superior rectus bridle suture is used to stabilize the eyeball and to ensure good exposure of donor area. Body of pterygium is dissected about 4 mm from limbus, down to bare the sclera and reflected over cornea. The pterygium head is avulsed using Lims forceps and crescent blade. Remnants over cornea were cleaned with crescent blade. Hemostasis was allowed to occur spontaneously without the use of cautery as littleoozing is useful as it helps in adherence of graft to the bed.[11]

As the donor site is usually superior or supero-temporal, sub conjunctival injection of local anesthetic solution is given to separate the conjunctiva from the tenon. Dissection between conjunctiva and tenon capsule is done so as to get a 1 mm oversize graft without tenon's tissue. The limbal edge of the graft was cut to contain a thin rim of corneal epithelium. The recipient bed is dried with cellulose sponge and graft was quickly flipped over to the sclera. Proper orientation was maintained, with the epithelium side up and the limbal edge toward the limbus.[11] Graft was pressed for 3–5 min. Graft stabilization was checked with a spear and speculum was removed. No sub conjunctival injection is given postoperatively because of fear of graft displacement. Pad and bandage were done for 24 h. Patients were called for follow-up after 1 day.

Post-operative Procedures

Bandage is opened after 24 h of surgery. Then antibiotic steroids combination eye drop and lubricating eye drop are prescribed for 4 weeks tapering and NSAID as and when required. Post-operative follow-up is done to see any recurrence or complications are present and are recorded. Data are recorded in tabulated form. The criterion for recurrence was determined as invasion of cornea more than 1 mm in diameter beginning from the limbus by fibrovascular tissue derived from the operation site.[12-14]

RESULTS

The present study was done on 100 eyes diagnosed with pterygium, of which 60 eyes (37 males and 23 females) operated with conjunctival autograft technique and 40 eyes (26 males and 14 females) were operated with bare sclera technique selected for the study. All patients were in the age group of 20–65 years. The recurrence rate in conjunctival autograft technique was 1 (1.67%) and

recurrence rate in bare sclera technique was 6 (15%) in this study. In this study, 71 (71%) eyes (patients) are having an outdoor occupation and 29 (29%) eyes (patients) having indoor occupation. Comparing the groups, revealed that recurrence was higher in the bare sclera group 6 cases out of 40 (15%) as compared to the conjunctival autograft group that is 1 case out of 60 (1.67%).

DISCUSSION

In this study, recurrence rate in conjunctival autograft technique was 1 (1.67%) and recurrence rate in bare sclera technique was 6 (15%). Khan *et al*.[10] also reported more recurrence in bare sclera 11 (36.6%) as compared to 3 (8.8%) in conjunctival autograft. In the study conducted by Alpay *et al*.,[15] recurrence was more in bare sclera technique 8 (38.09%) than conjunctival autograft 3 (16.6%). Results in our study are also in accordance of the results found by Ahmed *et al*.[16] where recurrence in bare sclera was 6 (40%) and conjunctival autograft was 1 (6%).

In this study, 71 (71%) eyes (patients) had an outdoor occupation and 29 (29%) eyes (patients) had an indoor occupation consistent with the study conducted by Beki-Bele *et al*., wherein he stated that outdoor occupation is an independent risk factor for the development of pterygium.[17] Study conducted by Salagar *et al*.[18] also showed prevalence of pterygium more in outdoor workers 96 (80%) then indoor workers 24 (20%).

CONCLUSION

This study stated that conjunctival autograft was a better treatment options compared to bare sclera technique as it has lesser recurrence rate and indicated that the incidence of pterygium is more common in patient having outdoor occupation compare to indoor.

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Original Article

Comparative Study of Topical 1% Voriconazole Versus 5% Natamycin in the Treatment of Fungal Corneal Ulcer

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Abstract

Introduction: Infective corneal ulcer is leading cause of corneal blindness in India among which fungal elements make a handful of cases. With lack of health facilities, poor hygiene, poor socioeconomic status, and literacy level, it is a major challenge to treat this infection. However, with advent of new topical antifungals, majority of cases can be treated and cured.

Materials and Methods: One hundred patients of diagnosed cases of fungal corneal ulcer after fulfilling the inclusion and exclusion criteria were randomly assigned into two groups. One group received topical 5% natamycin and the other group was treated with topical 1% voriconazole, and compared based on their effectiveness and statistically tabulated.

Results: The study included age group in 41–50 [34%] with males [78%] predominating, occupation being farmers [49%] and trauma [74%] as main predisposing factor. Both the drugs were well tolerated in study group. There was no significant statistical difference in time for re-epithelization of corneal defect, in infiltrate regression, reduction in signs or symptoms. In randomized natamycin group, corneal ulcer was healed with opacity in 84% of patients and in voriconazole group, it was healed in 78% of patients. In both the groups, epithelial defect was started healing by 4th weeks. Fungal organism was isolated in 55% of patients, in which *Fusarium* was the most common organism.

Conclusion: The present study did not reveal any significant statistical difference in final outcomes with topical natamycin compared with topical voriconazole treatment.

Key words: Corneal blindness, Drug efficacy, Fungal corneal ulcer, Natamycin, Voriconazole

INTRODUCTION

Corneal ulcer is defined as loss of corneal epithelium with underlying stromal infiltrate and suppuration associated with signs of inflammation, with or without hypopyon.[1]

In developing nations like India, cataract and corneal diseases are major cause of blindness.[2] According to the World Health Organization, world-wide, corneal diseases contribute a significant number. Coming to data in India, it is estimated to be around 6.6 million having poor vision due to corneal cause. It is expected that the number of individuals with corneal blindness in India will increase to 10.6 million by 2020.[3]

Fungal keratitis was first described by Leber in 1879.[4] Scarring of cornea as a result of suppurative keratitis is a leading cause of monocular preventable blindness worldwide. Corneal infection of fungal etiology is very common and represents 30%–40% of all cases of culture-positive infectious keratitis in South India.[5-12] Fungal keratitis is a major ophthalmic problem.[5,13] However, within tropics as many as two-thirds of ulcers may be due to filamentous fungi, for example, *Aspergillus*, *Fusarium,* and yeasts like candida. The treatment of fungal keratitis is generally more challenging than that of bacterial ulcers, and resulting visual impairment is, on average, more severe.

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Voriconazole 1% is a broad-spectrum, second-generation triazole antifungal agent with demonstrated efficacy in the treatment of invasive fungal infections caused by *Aspergillus* spp. and *Candida* spp.[14] Natamycin 5% is a tetraene polyene antifungal agent effective against variety of yeast and filamentous fungi. The present study is intended to compare the efficacy of topical 1% voriconazole with 5% natamycin ophthalmic solutions in fungal corneal ulcer patients in Tertiary Care Hospital.

METHODOLOGY

This study titled "A COMPARATIVE STUDY OF TOPICAL 1% VORICONAZOLE VERSUS 5% NATAMYCIN IN THE TREATMENT OF FUNGAL CORNEAL ULCER" was carried out in the department of ophthalmology, for a duration of 2 years after obtaining ethical clearance.

It was a comparative study with 100 subjects. Sample size was calculated from the past hospital record, on average the fungal keratitis is around 5/month. Hence, we adopted 100% enumeration technique (all diagnosed fungal corneal ulcer) for the 2 year period.

Inclusion Criteria

The following criteria were included in the study:

- All diagnosed cases of fungal corneal ulcers.

Exclusion Criteria

The following criteria were excluded from the study:

- Age <18 years
- Subjects with impending perforation
- Subjects with history of corneal scar in affected eye
- Subjects with previous keratoplasty in affected eye
- Subjects with known allergy to study medications
- Subjects with history of pregnancy or breastfeeding
- Subjects with no light perception in affected eye and.

Method of Collection of Data

One hundred patients of diagnosed cases of fungal corneal ulcer who fulfill the inclusion and exclusion criteria were included in this study. Data were collected using a piloted pro forma meeting the objectives of the study after an informed and written consent taken from all the patients.

A detailed history of each patient was obtained regarding the age, sex, place, and occupation and about all the risk factors such as history of trauma, diabetes, and prior use of any topical steroids. Patients were randomized to receive topical 5% natamycin or 1% voriconazole after determination of eligibility.

All the study subjects had a thorough ophthalmic evaluation which included a calibrated slit lamp examination to assess

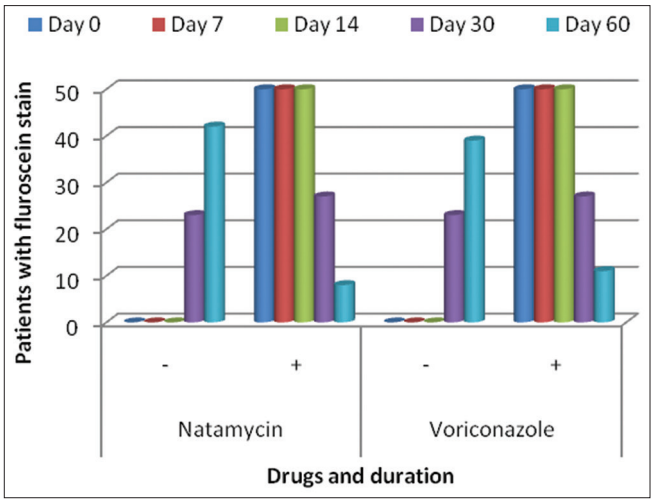

Figure 1: fluorescein stain am among two groups and progression after starting treatment

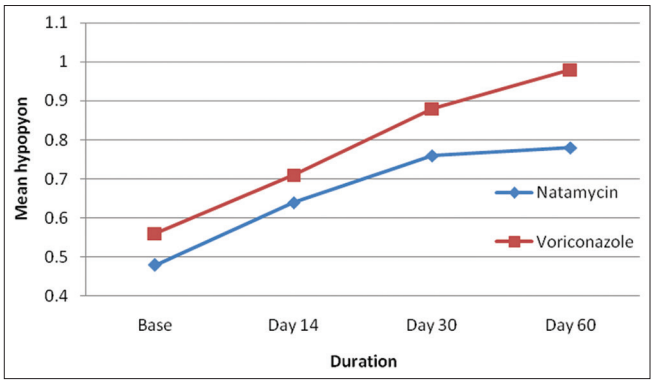

Figure 2: Mean hypopyon among two groups

the epithelial defect with fluorescein staining, depth, stromal infiltration, and hypopyon. Corneal lesion was measured using a vertical illumination source models. First, the slit is rotated to coincide with the axis that you want to measure. Then, the slit beam height is reduced or lengthened to match the lesion. The measurement is read from a slit length display window on the illumination arm. Corneal ulcer was graded using a modification of Jones's grading for the severity of microbial keratitis. It was graded as Grade 1 (2 mm area, with superficial one-third of depth), Grade 2 (2–6 mm, with superficial two-thirds of depth), and Grade 3 (>6 mm, with full-thickness depth). The best-corrected visual acuity (BCVA) of eye was tested using Snellen chart at enrolment, 2nd day, 1st week, 2nd week, 1st, month and 2nd month from enrolment.

All subjects were taken up for corneal scrapings. First, the ulcer was stained with fluorescein stain then using standard techniques, corneal scraping was performed to all corneal ulcer patients under aseptic condition using 22 gauge needle following the instillation of local anesthesia (proparacaine

eye drops). The material collected from the advancing edge and margin of the ulcer and it was obtained by multiple sites. It was inoculated directly onto blood agar, chocolate agar, for bacteria, and Sabouraud's dextrose agar for fungal culture. Two smears were made onto two slides. One slide was stained with Gram's stain and the other with 10% KOH preparation for direct microscopic examination.

If all inclusion criteria and no exclusion criteria were met, the subjects were enrolled in the study. Subjects were randomized to receive topical 5% natamycin or 1% voriconazole. Assessments of clinical characteristics (infiltrate, epithelial defect size), hypopyon, and BCVA were performed at enrolment, 2nd day, 1st week, 2nd weeks, 1st month, and 2nd months. Visual acuity measurements were performed using Snellen chart.

Statistical Methods Applied

Data were analyzed using Statistical Presentation System Software for windows (version 20.0).

Following statistical methods were employed

- Descriptive statistics
- Contingency coefficient analysis
- Chi-square test
- *t*-test – independent samples
- Repeated measures analysis of variance.

RESULTS

Among the 100 cases that were included in the study, majority of the cases, that is, 34 cases (34%) were in the age group of 41–50 years. This is followed by 25 (25%) cases in the age group of 51–60 years. Among the 100 patients, 78 (78%) were male and 22 (22%) were female. Out of 100 patients, 49 (49%) were farmers, followed by 15 (15%) coolies and 13 (13%) homemakers, 6 (6%) business, 5 (5%) shopkeepers, 4 (4%) office workers, and 2 carpenter and conductor one each of driver, mechanic, tailor, and teacher. Seventy-four (74%) are from rural and rest 26 (26%) from urban. About 74% of patients had history of trauma in this study. About 16% of patients had dacryocystitis, 17% of patients had diabetes mellitus, and 5% of patients were using topical steroids.

Many patients gave history of trauma with various agents. The majority of patients had trauma with vegetative matter [Table 1]. In our study, it showed that in both the groups, all were presented with redness and pain at presentation. In randomized natamycin group, redness was absent in 30 (60%) patients at 1 month and in voriconazole group, it was absent in 29 (58%) patients. At 2 months, it was absent in 42 (84%) patients in natamycin group and in voriconazole group, it was absent in 39 (78%) patient. With regard to pain, it showed that at 2 weeks, 46 (92%) patients were having pain in randomized natamycin group and 48 (96%) patients in voriconazole group. At 1 month, pain was absent in 32 (64%) patients in natamycin group and was absent in 31(62%) patients in voriconazole group. At 2 months, 3 (6%) patients were having pain in natamycin and 6 (12%) patients in voriconazole group [Table 2].

Table 3 shows 16 (32%) patients were presented with Grade 1 corneal ulcer in randomized natamycin group and 15 (30%) patients in voriconazole group. By the period of 1 month, 15 (30%) patients were healed in natamycin group and 13 (26%) patients in voriconazole group.

At enrolment, in natamycin group, 33 (66%) patients were presented with Grade 2 corneal ulcer and in that 8 (16%) patients were healed by 1 month and 5 (10%) patients had corneal perforation. In voriconazole group, 34 (68%) patients were presented and 10 (20%) patients were healed by 1 month and 6 (12%) patients had corneal perforation. By the end of 2 months, 7 (14%) patients had corneal perforation in natamycin group and 10 (20%) patients had perforation in voriconazole group with Grade 2 corneal ulcer [Table 4].

In each group, one patient was presented with Grade 3 corneal ulcer with full-thickness infiltrate and had perforation at 1 month [Table 5]. Figure 1 shows graphical explanation of fluorescein staining. It was negative in 23 (46%) patients in natamycin group at 1 month and 42 (84%) patients were negative at 2 months and 39 (78%) patients were having fluorescein stain negative in voriconazole group at 2 month.

In the present study, at enrolment, mean hypopyon in natamycin group was 0.48 and in voriconazole group, it was 0.56. At 1 month, mean hypopyon in natamycin group was 0.76. In voriconazole group, mean hypopyon at 1 month was 0.88. At 2 months, mean hypopyon in natamycin group was 0.78 and in voriconazole group, it was 0. 98, as depicted in Figure 2.

Table 1: Nature of trauma

Nature of trauma	Number of patients
Sugar cane leaf	15
Ragi plant	10
Paddy leaf	12
Animal tail	10
Foreign body	14
Stick injury	08
Stone	05
Total	74

Table 2: Progression of redness/pain in both the groups

Examination day	Natamycin				Voriconazole			
	Redness	No redness	Pain	No pain	Redness	No redness	Pain	No pain
Day 0	50	0	50	0	50	0	50	0
Day 14	45	5	46	4	47	3	48	2
Day 30	20	30	18	32	21	29	19	31
Day 60	8	42	3	47	11	39	6	44

Table 3: Grade 1 (with 2 mm area with anterior stromal infiltration)

Examination day	Natamycin		Voriconazole	
	No. of patients with ulcer	No. of patients with healed opacity	No. of patients with ulcer	No. of patients with healed opacity
Day 0	16	0	15	0
Day 2	16	0	15	0
Day 7	16	0	15	0
Day 14	16	0	15	0
Day 30	1	15	2	13
Day 60	0	1	0	2

Table 6 shows that the visual acuity at enrolment in both natamycin and voriconazole group was in the range of CF 1 m to CF 5 m in 43(86%) patients. In randomized voriconazole group at 1 month, 2 (4%) patients had visual acuity in the range of 6/36–6/24. In randomized natamycin group, the visual acuity was in the range of 6/36–6/24 in 15 (30%) patients and the range of 6/18–6/9 was present in 15 (30%) patients at 2 months. In randomized voriconazole group at 2 months, the visual acuity was in the range of 6/36–6/24 in 15 (30%) patients and the range of 6/18–6/9 was present in 13 (26%) patients.

Figures 3, 4 and 5 fungal organism was isolated in 55 patients and in which *Fusarium* was 26 (47.27%) followed by *Aspergillus* 19 (34.55%) and *Candida albicans* 10 (18.18%). There was no fungal growth in 45 patients.

Twenty-three patients surgical treatment was done. Dacryocystectomy was done in 16 patients. Conjunctival hooding was done for four patients and debridement was done for three patients. In 77 patients, surgical treatment was not done. Out of 50 in randomized natamycin group, 8 (16%) patients had corneal perforation. In randomized voriconazole group, 11 (22%) patients had corneal perforation [Figure 6].

Figure 3: *Fusarium* growth on SDA

Figure 4: *Aspergillus* growth on SDA

DISCUSSION

In this present study, most common age group presented with corneal ulcer was 41–50 years (34%) which was supported by Bharati *et al*.[5] study, in which the commonest age group was between 31 and 50 years and in Nath *et al*.[15] study, the most commonly affected age group was 41–50 years.

Table 4: Grade 2 (with 2-6 mm area with mid stromal infiltration)

Examination day	Natamycin			Voriconazole		
	No. of patients with ulcer	No. of patients with healed opacity	No. of patients with perforation	No. of patients with ulcer	No. of patients with healed opacity	No. of patients with perforation
Day 0	33	0	0	34	0	0
Day 2	33	0	0	34	0	0
Day 7	33	0	0	34	0	0
Day 14	33	0	0	34	0	0
Day 30	20	8	5	18	10	6
Day 60	0	18	2	0	14	4

Table 5: Grade 3 (with>6 mm area with full thickness)

Examination day	Natamycin			Voriconazole		
	No. of patients with ulcer	No. of patients with healed opacity	No. of patients with perforation	No. of patients with ulcer	No. of patients with healed opacity	No. of patients with perforation
Day 0	1	0	0	1	0	0
Day 2	1	0	0	1	0	0
Day 7	1	0	0	1	0	0
Day 14	1	0	0	1	0	0
Day 30	0	0	1	0	0	1

Table 6: BCVA among both the groups

Visual acuity	Natamycin			Voriconazole		
	Day 0	Day 30	Day 60	Day 0	Day 30	Day 60
6/18–6/9	0	0	15	0	0	13
6/36–6/24	0	3	15	0	2	15
Counting fingers (CF) 6 mt–6/60	1	20	9	1	19	8
CF 1 mt–CF 5 mt	43	19	3	43	18	3
HM-PL	6	8	8	6	11	11

BCVA: Best-corrected visual acuity

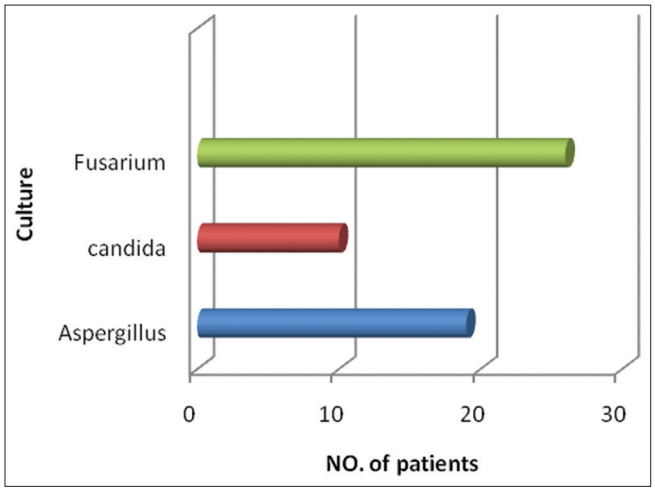

Figure 5: Culture findings

In the present study, males (78%) were predominantly affected than females (22%). In Srinivasan *et al.*[10] study, 61.3% were male and 38.7% were female. In the other similar studies, male preponderance ranged between 65% and 68%.

In this study, majority of the patients (49%) were farmers, followed by coolie (15%), homemaker (13%) and then business (6%) and others. By the nature of their outdoor activities, men are more vulnerable to disease. In Bharati *et al.*[5] study, farmers contributed to 64.5% followed by homemaker (5.1%). In Srinivasan *et al.*[10] study, the majority of ulcer patients were agricultural workers, homemakers, or laborers which are in favor of the present study.

In this study, 74% patients were from rural areas and 26% from urban areas. In Bharati *et al.* study, 80.27% patients were from rural areas. The most common predisposing factor in the present study is trauma (74%) and in Bharati *et al.* study, corneal trauma was identified in 92.15%. In Tilak *et al.*[16] Mycotic keratitis in India study, ocular trauma was predisposed to infection in 54% of patients. In the study done by Chander *et al.*[17] in Chandigarh, 76.62% were from rural background and majority of them (89.83%) were farmers which supports the present study.

In this present study, dacryocystitis was present in 16% of patients. In Nath *et al.* study, blocked nasolacrimal duct was the local predisposing factor in 11.1% of cases which support the present study. In the present study, diabetes mellitus was present in 17% of patients. In Bharati *et al.* study, 15.71% of patients had diabetes mellitus which is in favor of the present study. Diabetes was a significant systemic predisposing factor in fungal infections in 11.1% cases in Nath *et al.* study. The use of topical steroids was present in 5% of cases in this study. In Bharati *et al.* study, the use of corticosteroids associated with development of

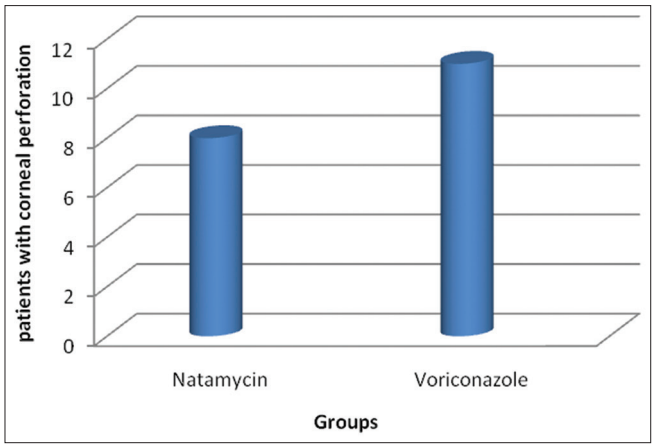

Figure 6: Number of eyes with perforation among the two groups

fungal keratitis accounted for 7.85% patients which support the current study. Similarly in Srinivasan *et al*. study, 8.0% were on corticosteroids. The probable reason for this was that these drugs are easily available over counter in our country and amount of illiteracy level.

All patients in this study group were positive for 10% KOH wet mount because that was the chosen inclusion criteria for the recruitment of patients in the study. Out of 100 patients, 55 (55%) were fungal culture proven and the remaining 45 (45%) were culture negative. In Nath *et al*. study, 65% of patients showed culture positive. Out of the 100 cases of corneal ulcer, fungal growth was seen in 32 eyes in Dutta *et al*. study.[1] In the study done by Chander *et al*. in Chandigarh, 53.12% were positive on fungal culture. In Ghana study, 57.3% were cultures positive,[18] which are in favor of the present study.

In this study, *Fusarium* was the most common organism (47.27%), followed by *Aspergillus* (34.55%) and *C. albicans* (18.18%). This is supported by Srinivasan *et al*. study where fungal isolates cultured from corneal ulcers, *Fusarium* spp, was the most common followed by *Aspergillus* spp, and the remaining organisms. Among 100 patients, 19 (19%) patients had corneal perforation. In Nath *et al*. study, 12.1% cases had perforation. In randomized natamycin group, 8 (16%) patients had corneal perforation and in voriconazole group 11 (22%) patients had perforation. This was statistically not significant ($P = 0.44$).

CONCLUSION

In this study of fungal keratitis, the analysis showed no significant statistical difference in time for re-epithelization of corneal defect, no difference in infiltrate regression. There was no significant statistical difference in time taken for resolution of hypopyon, final visual acuity outcome, or adverse events between the topical natamycin treatment compared with topical voriconazole.

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Original Article

Evaluation of Diabetic Dyslipidemia in Patients with Type 2 Diabetes Mellitus

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Abstract

Introduction: Type 2 diabetes mellitus (DM) is the most common metabolic disorder in the world. Patients with diabetic dyslipidemia are more prone for developing macrovascular complications compared to subjects without DM. Hence, morbidity and mortality are high among patients with DM.

Aim: The aim of this study was to study the prevalence and pattern of diabetic dyslipidemia in the study population so as to intensify treatment to achieve optimum glycemic and lipid control.

Materials and Methods: The study was carried out on 50 patients with type 2 DM who attended the Department of General Medicine, KIMSH and research center, Bangalore between the period of January 1 to March 1 , 2022, it was a cross-sectional study. Statistical analysis was done using Epi Info software. Chi-square test was done to see the statistical significance of difference between males and females, $P < 0.05$ was considered significant in this study.

Results: Among the study population, 46% were male and 54% were female, mean age of the study population was 53 ± 7 years. About 44% (n = 22) of the patients had higher triglyceride (TG) levels and 54% (n = 38) had optimum TG levels of <150 mg/dl. About 60% (n = 30) had high low-density lipoprotein cholesterol (LDL-C) levels, whereas 40% (n = 20) had optimum LDL-C levels of <100 mg/dl. About 98% (n = 49) had low high-density lipoprotein cholesterol (HDL-C) values of <40 mg/dl. About 44% (n = 32) had Non-HDL (NON-HDL) levels of >130 mg/dl, whereas 56% (n = 28) had optimum levels of <130 mg/dl. The mean TG level was 173.76 ± 97.68 mg/dl, mean LDL-C was 103.18 ± 38.03 mg/dl, mean HDL-C was 31.54 ± 9.91 mg/dl, and mean NON-HDL level was 123.44 ± 42.41 mg/dl. The mean fasting blood sugar was164.66 ± 71.37 mg/dl and mean postprandial blood sugar was 242.54 ± 86.09 mg/dl.

Conclusion: The pattern of diabetic dyslipidemia high TG, high LDL-C, and low HDL-C is still prevalent among patients with type 2 DM which requires early screening and intense glycemic and lipid control to prevent macrovascular complications.

Key words: Diabetes mellitus, Dyslipidemia, Triglyceride

INTRODUCTION

Diabetes mellitus (DM) is the most common metabolic disorder in the world. According to the IDF, 537 million people in the world live with diabetes as of 2021.[1,2] In most countries, the number of individuals with diabetes is steadily increasing. China has the largest number of people with diabetes in the world (140.8 million), followed by India with 74.1 million.[1,2] DM is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both leading to microvascular and macrovascular complications.[1,2] Among the macrovascular complications, cardiovascular diseases (CVDs) contribute to significant morbidity and mortality in patients with type 2 DM. Dyslipidemia is found to be one of the major risk factors for atherosclerotic CVD in type 2 DM. A triad of high Triglyceride (TG), low high-density lipoprotein (HDL), and high low-density lipoprotein (LDL) particles is observed in patients with type 2 DM which is referred to as "Atherogenic Diabetic Dyslipidemia (ADD)," as shown in Figure 1. Insulin resistance at the level of adipocyte causing increased free fatty acid efflux is thought

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to be central to the pathogenesis of ADD.[3] American Diabetes Association (ADA)[4] guidelines recommend maintaining serum TG below 150 mg/dl, LDL cholesterol below 100 mg/dl, and HDL cholesterol of more than 40 mg/dl in males and 50 mg/dl in females. This study evaluates the prevalence and pattern of dyslipidemia in patients with type 2 DM to achieve better treatment goals that may reduce risk of CVD in this population.

MATERIALS AND METHODS

The present cross-sectional study was conducted at the department of General Medicine, Kempegowda Institute of Medical Sciences And Research Center, Bangalore from January 1 to March 1 , 2022, over a period of 2 months. The study was carried out on 50 patients with type 2 diabetes. Informed consent was taken from all the patients.

Inclusion Criteria

Known case of type 2 diabetes, including recently diagnosed cases.

Exclusion Criteria

Patients with the following conditions were excluded from the study:

- Type 1 diabetes on insulin
- Hypothyroid patients
- Obesity
- Diabetic patients with chronic kidney disease
- Nephrotic syndrome
- Patients on lipid lowering agents.

The diagnosis of diabetes was made by ADA criteria[4]

Both fasting and postprandial blood sugars were estimated using hexokinase method. HBA1C was measured by immunoturbidometry method. Lipid profile panel was considered as follows as per our hospital laboratory protocol.

Total cholesterol:

- <200 mg/dl desirable
- 200–239 borderline high
- >240 high.

Measured by CHOD-PAP method.

TG:

- <150 mg/dl normal
- 150–199 borderline high
- 200–449 high
- >500 very high.

Measured by GPO-PAP method.

HDL

- <40 mg/dl low
- >60 mg/dl high.

LDL

- <100 mg/dl optimal
- 100–129 mg/dl above optimal
- 130–159 borderline high
- 160–189 high
- >190 very high.

HDL and LDL both measured by DIRECT method.

Statistical Analysis

The data were analyzed using various statistical methods such as percentage, proportion, and tables using Epi Info software. Chi-square test was used to see the statistical significance of difference between males and females, $P < 0.05$ was considered significant for the purpose of this study.

RESULTS

The study population comprised 50 patients of type 2 diabetes with 23 (46%) males and 27 (54%) females. The mean values of biochemical parameters are as shown below.

Twenty-two patients have TG level >150 mg/dl which comprise 44% of the total study population.

Thirty patients have LDL-C level >100mg/dl which comprise 60% of the total study population.

DISCUSSION

Our research reveals information on the prevalence and pattern of dyslipidemia in the diabetic population seen by us in our day-to-day clinical practice. The mean values of the biochemical parameters taken for our study are shown in Table 1. Our study shows that only 40% ($n = 20$)

Table 1: Mean biochemical values

Mean values in mg/dl	Total patients *n*=50	Male *n*=23	Female *n*=27
FBS	164.66±71.37	161.43	167.40
PPBS	242.54±86.09	237.86	246.51
TC	154.26±41.64	141.82	164.85
TG	173.76±97.68	152.26	192.07
HDL-C	31.54±9.91	30.69	32.25
LDL-C	103.18±38.03	96.47	111.42
NON-HDL	123.44±42.41	112.69	132.59

FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, TC: Total cholesterol, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, NON-HDL: Non-high-density lipoprotein

of the patients had their LDL-C levels within the target range and 60% (n = 30) of the study population had LDL-C levels beyond the target range, as shown in Table 2. These results are comparable to the data from Kennady *et al*.[5] who found that only 45% of those with diabetic dyslipidemia are at LDL-C goal; similarly, Jayaram *et al*.[6] have shown that only 43.91% patients achieved LDL-C goal in a study from India. Control of other lipid parameters such as serum TG and HDL-C levels were also found to be inadequate with only 56% (n = 28) of the patients achieving target TG levels and 44% (n = 22) of the patients had TG levels >150 mg/dl, respectively, as shown in Table 3. About 98% of the patients have HDL-C level <40 mg/dl and 2% had >60 mg/dl, as shown in Table 4; HDL-C levels have been found to be significantly lower in an our study population.[7-10] We also evaluated the non-HDL levels in our study population, 44% (n = 22) had HDL-C >130 mg/dl, as shown in Table 5, because non-HDL cholesterol measures the apo B containing lipoproteins, it can serve as an additional tool to assess cardiovascular risk.[11] As mentioned earlier, a triad of high TG, low HDL, and high LDL is referred to as atherogenic diabetic dyslipidemia; our study correlates with the above findings hence putting our study population under significant cardiovascular risk.[7-10,12,13] In our study, there no was significant differences between the lipid parameters among male and female gender, $P > 0.05$; hence, both males and females were at an equal risk of acquiring CVD.

Table 2: LDL-C levels

LDL-C in mg/dl	TP n=50 (%)	Male n=23	Female n=27
<100	20 (40)	11	9
100–129	15 (30)	4	11
130–159	10 (20)	7	3
160–189	4 (8)	1	3
>190	1 (2)	0	1

LDL-C: Low-density lipoprotein cholesterol

Table 3: Serum triglyceride levels in DM

Serum TG in mg/dl	TP n=50 (%)	Male n=23	Female n=27
<150	28 (56)	15	13
150–199	4 (8)	1	3
200–499	18 (36)	7	11
>500	0	0	0

TG: Triglyceride, DM: Diabetes mellitus

Table 4: HDL-C levels

HDL-C in mg/dl	TP n=50	Male n=23	Female n=27
<40	49 (98%)	22	27
>60	1 (2%)	1	0

HDL-C: High-density lipoprotein cholesterol

Table 5: NON-HDL levels

NON-HDL in mg/dl	TP n=50 (%)	Male n=23	Female n=27
<130	28 (56)	14	14
>130	22 (44)	9	13

NON-HDL: Non-high-density lipoprotein

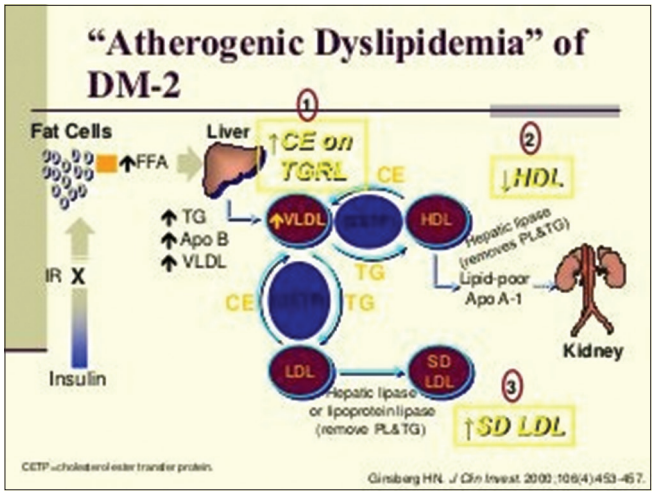

Figure 1: Atherogenic diabetic dyslipidemia mechanism

CONCLUSION

Our present study concludes that there was significantly higher levels of serum LDL-C level, serum TG and non-HDL levels in our study diabetic population and low levels of serum HDL-C levels which contribute to increased cardiovascular, cerebrovascular, and peripheral arterial morbidity and mortality. Hence, efforts should be intensified in the area of glycemic control, lipid lowering, and lifestyle modification to reduce the risk of morbidity and mortality in diabetic patients.

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