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Case Report

Rare Pancreatic Anomaly in an Adult

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Abstract

Annular pancreas is a neonatal condition causing duodenal obstruction and is associated with other congenital anomalies such as Down's syndrome and intestinal atresia. Its estimated frequency is one case out of 1200–1500 live births. It occurs due to failure of rotation of ventral bud with duodenum causing partial or complete ring around duodenum. Annular pancreas is rare in adults with a reported incidence of 0.005–0.015%. Contrast-enhanced computed tomography abdomen, endoscopic ultrasound, and magnetic resonance cholangiopancreatography help in making the diagnosis of the annular pancreas. Here, we report a case of annular pancreas in an adult and how we managed it.

Key words: Adult, Annular pancreas, Rare

INTRODUCTION

Annular pancreas is a rare congenital condition where the second part of the duodenum is surrounded by a ring of pancreatic tissue continuous with the head of the pancreas. Tiedemann reported this congenital anomaly in 1818, later named as "annular pancreas" by Ecker because of its ring-like effect around the duodenum.[1,2]

Its estimated frequency is one case out of 12000–15000 live births and is often associated with other congenital anomalies such as Down's syndrome, tracheoesophageal fistula, intestinal atresia, pancreatic division, and pancreaticobiliary malrotation.[1,3]

Here, we report a case of the symptomatic annular pancreas in an adult and how we managed it.

CASE REPORT

A 41-year-old male presented to us with complaints of the upper abdominal pain and vomiting, 2–3 episodes per day, containing food particles for 15 days. He is a known diabetic, alcoholic, and smoker. A chest and abdominal X-ray [Figure 1a and b] showed a prominent gastric fundal shadow. Contrast-enhanced computed tomography (CECT) was done, showing a mass encircling the second part of the duodenum suggestive of the annular pancreas [Figure 2a and b].

Esophagoduodenoscopy was done, which confirmed the narrowing at the second part of the duodenum [Figure 3a and b]. Therefore, the patient underwent midline laparotomy and intra-operative findings were-dilated stomach with narrowing of the duodenum [Figure 4a and b]. He underwent gastrojejunostomy along with jejunojejunostomy. Post-operative course was uneventful and he was discharged on post-operative day 6. After 6-months of follow-up, the patient tolerated normal diet and has gained weight with no recurrence of any symptoms.

DISCUSSION

At the 5th week of gestation, a single dorsal and two ventral buds (which rapidly fuse) develop as an outgrowth of primitive foregut. By the 7th week of gestation, expansion of duodenum causes ventral bud to rotate and pass behind duodenum from right to left and fuse with dorsal bud. Ventral bud forms inferior or part of the uncinate process and inferior head of the pancreas and dorsal bud gives rise to tail and body. The main pancreatic duct is formed by

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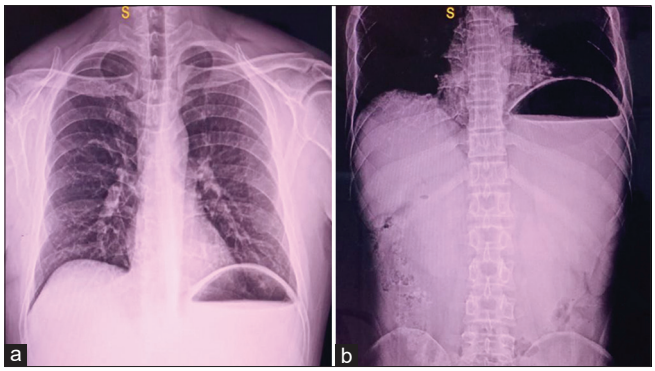

Figure 1: (a and b) Chest X-ray and Abdominal X-ray showing prominent gastric shadow

the fusion of the ducts of two buds. Failure of ventral bud to rotate with duodenum leading to the envelopment of duodenum causes annular pancreas [Figure 5]. Of annular pancreas cases, 25% form a complete ring and 75% have a partial ring. The formation of the annular pancreas occurs probably by one of two mechanisms proposed by Lecco and Baldwin but neither theory explains all cases of annular pancreas.[4,5]

Annular pancreas is a congenital anomaly that occurs at a frequency of 1:20,000 births. Annular pancreas affects both sexes with a slight male preponderance, which has been a contentious issue. The most of the cases of the

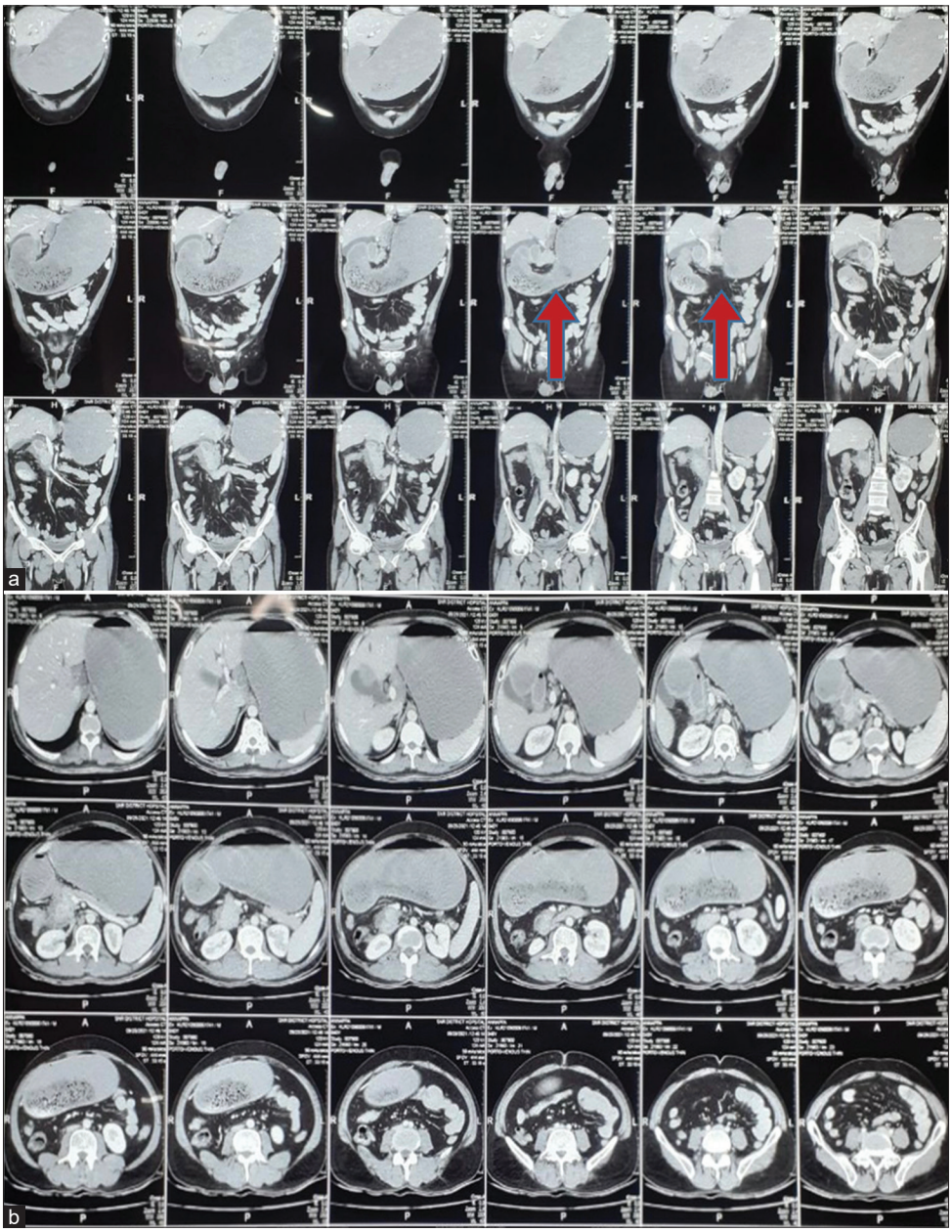

Figure 2: (a and b) CECT abdomen and pelvis showing narrowing of second part of duodenum (Marked by arrow) because of annular pancreas

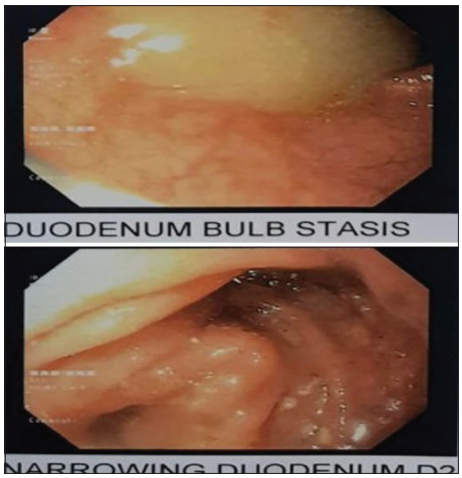

Figure 3: Upper GI endoscopy showing narrowing at second part of duodenum

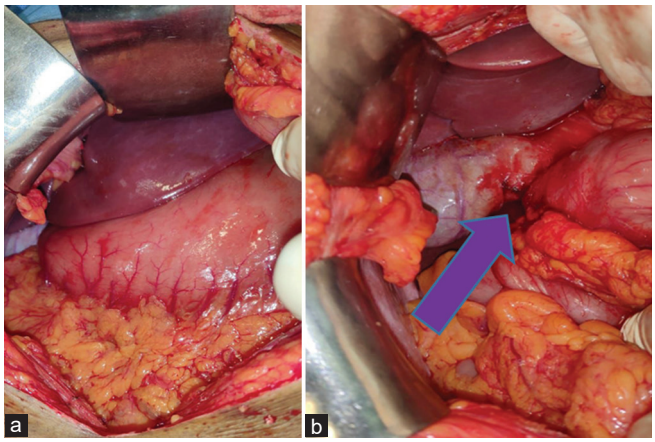

Figure 4: (a) Intra-operative finding - Dilated stomach secondary to obstruction by annular pancreas, (b) Narrowing of duodenum (Marked by arrow mark)

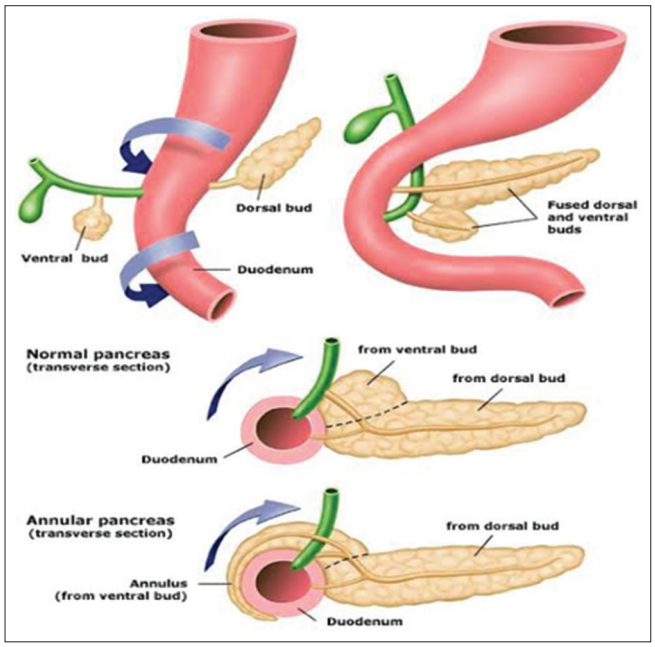

Figure 5: Formation of annular pancreas

annular pancreas in adults remain asymptomatic but when symptomatic, presentation is usually in the third to sixth decade with cramping epigastric pain and postprandial fullness and these symptoms are relieved with vomiting. The clinical manifestations were related to the degree of duodenum compression by annular pancreas, whether it compresses common bile duct (CBD), and the degree of compression of CBD. The reported incidence in adults varies from 0.005% to 0.015%.[2,5-7]

Associated conditions include peptic ulcer diseases, acute pancreatitis, pancreatic head carcinoma, biliary obstruction with jaundice, and gastric outlet obstruction with the most common being pancreatitis.[2] Its association with malignancy is rare as it was described only 14 times in English literature.[8] A double bubble sign on a plain radiograph is seen in this condition. CECT abdomen, endoscopic ultrasound, and magnetic resonance cholangiopancreatography (MRCP) help in making the diagnosis of the annular pancreas with MRCP being the best non-invasive method. Endoscopic retrograde cholangiopancreatography can make a specific diagnosis but is an invasive method.[5]

Surgery is the definitive treatment for the annular pancreas which includes bypass surgery, that is, duodenoduodenostomy in neonates and children, duodenojejunostomy or gastrojejunostomy in adults. Laparoscopic gastrojejunostomy is a feasible option for treating the annular pancreas. Resection of the annular pancreatic tissue is avoided as it is associated with several complications such as pancreatitis, pancreatic fistula formation, and incomplete relief of obstruction, as well as a lower rate of permanent cure which makes bypass surgeries treatment of choice.[5,9,10]

CONCLUSION

Although the incidence of the annular pancreas in adults is very low, it should be kept in mind as a differential diagnosis. Surgical treatment, that is, Bypass procedure is the treatment modality for the symptomatic annular pancreas.

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Case Report

Sickle Cell Crisis presenting as Acute Reversible Pulmonary Arterial Hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a relatively frequent and severe complication of sickle cell (SC) disease and an independent risk factor for mortality. We report case of SC trait presented with acute onset dyspnea class IV, hypoxia, and moderate PAH with dilated right atrium and right ventricle on 2DECHO. Normal computed tomography Pumonary angiography on 2DECHO and normal CT pulmonary angiography. He was treated with hydration, O_2, hydroxyurea, and folic acid. The patient improved symptomatically and 2DECHO was normalized.

Key words: Hydration, Reversible pulmonary arterial hypertension, Sickle cell crisis

INTRODUCTION

Sickle cell disease (SCD) encompasses a group of hemoglobinopathies characterized by amino acid substitutions in the beta-globin chain. The most frequently occurring form of SCD is caused by homozygous presence of hemoglobin S (HbSS). Pulmonary hypertension (PH) is a relatively frequent and severe complication of SCD and an independent risk factor for mortality.[1]

Prevalence

Echocardiographic screening studies have identified evidence of elevated pulmonary pressures, defined as a tricuspid regurgitant jet velocity ≥2.5 m/s (equivalent to a pulmonary artery systolic pressure of approximately 36 mmHg), in 30–40% of HbSS and 10–28% of HbSC adults.[2]

Pathogenesis

The exact pathogenesis of Pulmonary arterial hypertension (PAH) in SCD is not known, but a number of potential contributing factors have been implicated, including endothelial injury from recurrent sickling, acute and chronic inflammation, hypercoagulability, chronic intravascular hemolysis, and altered bioavailability of the potent vasodilator nitric oxide (NO). Vascular remodeling caused by chronically elevated left heart pressures from diastolic dysfunction may also contribute, similar to PH group 2, which is purely due to left heart disease.[3]

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CASE REPORT

A 40-year-old male known case of Sickle cell trait was on hydroxyurea, folic acid, and tablet sodamint, which was presented with acute onset dyspnea of 2 days duration without fever, cough, orthopnea, leg edema, and angina. Physical examination revealed tachycardia with pulse rate of 130/min, regular and good volume, blood pressure was 100/70 mmHg, no cyanosis, clubbing, chest was clear, CVS-S1, S2 was normal and no murmur, Spo_2 was 88% at room air, ECG showed sinus tachycardia with T wave inversion in anterior leads [Image 1], and 2DECHO [Image 2] showed dilated right atrium/right ventricle (RA/RV) with moderate PAH (65 mmHg). Acute pulmonary thromboembolism (PTE) was suspected, so computed tomography pulmonary angiography (CTPA) was done. To surprise, it was normal. Hence, the patient was treated with hydration, O_2, low molecular weight heparins,

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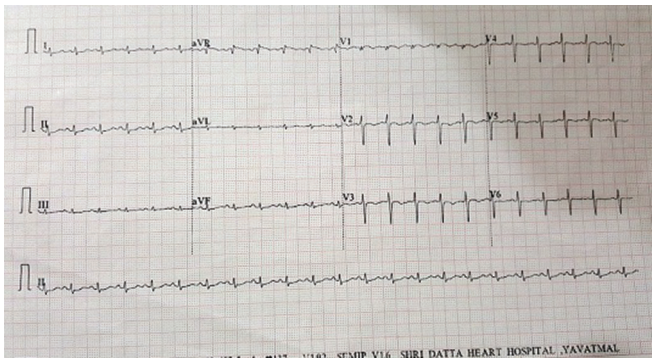

Image 1: ECG showing sinus tachycardia and RV strain

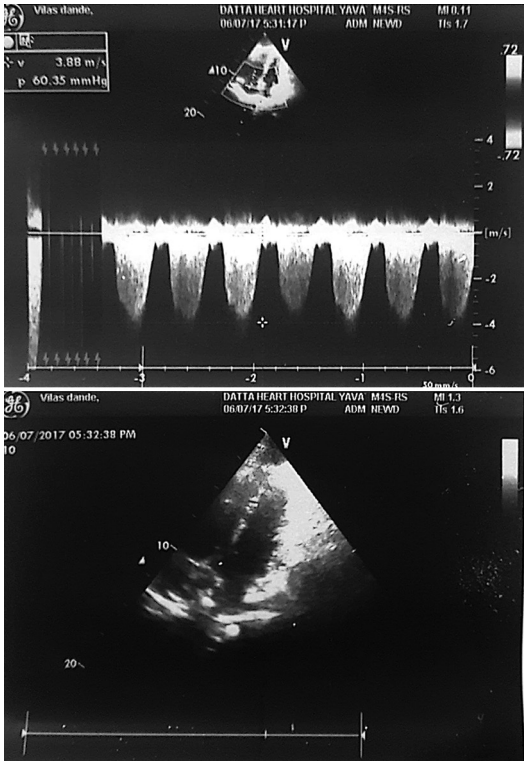

Image 2: Dilated RA and RV with moderate PAH

hydroxyurea, and supportive drugs. The patient improved symptomatically, O_2 was stopped, and repeat 2DECHO [Image 3] showed normalization of dilated RA/RV and pulmonary arterial pressure (PAP).

We conclude that this normalization of PAP was due to normalization of PVR which might have increased due to occlusion of capillaries by deformed red blood cells.

DISCUSSION

PAH is defined as an elevated mean arterial pressure ≥25 mmHg at rest.[1,4] PAH has several etiologies and can be a progressive, fatal disease, if untreated.

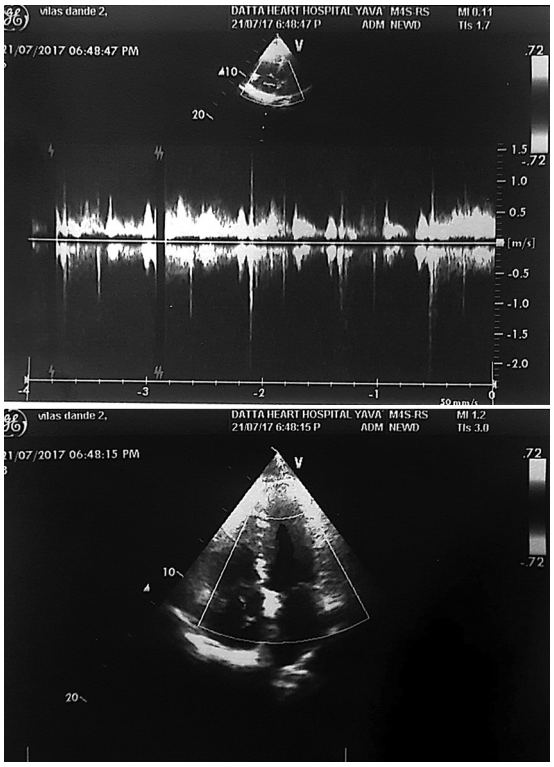

Image 3: Follow up ECHO showing normalisation of RA, RV and PA pressure

The cause of PH, which has been reported in 20–32% of SCD patients, is multifactorial, with contributing factors including hemolysis, impaired NO bioavailability, chronic hypoxemia, high cardiac output, thromboembolism, and parenchymal and vascular injury caused by sequestration of sickle erythrocytes, chronic liver disease, and asplenia.[3] There are very few instances, where PAH is reversible like acute PTE.

We report a case, where the patient presented with acute dyspnea and moderate PAH. The clinical presentation was like acute PTE, but CTPA was did not show any thrombus. PAH regressed to normal, 2DECHO picture of dilated RA and RV normalized with hydration and oxygenation. Transesophageal echo showed intact IAS and no evidence of sinus venosus ASD. This patient was known case of sickle cell (SC) trait, so we conclude that acute reversible PAH was secondary to SC crisis. We have searched in the literature for PAH in SCD, it showed chronic PAH but have not seen a case which presented like this.

There is a one case series of six patients by Abraham *et al.* which mention about regression of PAH by oxygen supplementation in Chronic Bronchitis. In my case also prolong, oxygenation had helped in PAH regression.[5]

Intensification of hydroxyurea and exchange transfusion is mainstay of treatment, we have insufficient data to explain, whether prolonged oxygenation can be a therapy for chronic PAH.

CONCLUSION

Acute reversible PAH is seen in acute PTE which can improve with early thrombus resolution. Similar finding are observed in sickle cell crisis. Early treatment of crisis can help to normalize PAP and to prevent development of chronic PAH. In our observation, this is a second cause of acute reversible PAH after acute PTE.

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Case Report

Fibromyxoma of Gingiva – A Rare and Distinct Clinicopathological Entity

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Abstract

The intraoral fibromyxoma is an uncommon, slowly growing, benign mesenchymal tumor. It can occur in two different types, namely, odontogenic fibromyxomas and soft-tissue fibromyxomas. The fibromyxomas are rare in gnathic region, which can occur in all age groups, but they are most common in the 2nd and 3rd decades of life. Most frequent locations were the cheek, floor of the mouth, and palate. We present a rare case report of oral soft-tissue myxoma in a 23-year-old female patient who presented with a soft, exophytic round mass on the palate. An excisional biopsy was performed under local anesthesia. Histopathological diagnosis of a fibromyxoma was established. A follow-up of 6 months was done and no complication or episodes of recurrences were noted.

Key words: Fibromyxoma, Histopathology, Neoplasm

INTRODUCTION

Fibromyxoma is a rare slow-growing benign neoplasm, usually occurring in the 2nd and 3rd decades of life, rarely seen in children or adults over 50 years of age. The term was first introduced by Rudolph Virchow in 1863 to describe it as an abdominal soft-tissue lesion. It is an uncommon, locally infiltrative benign tumor of the connective tissue, arising in bones and soft tissues.[1,2] Fibromyxomas of orofacial region arise from the mesenchymal tissue of the dental follicle, but soft-tissue counterparts arise from suppurative structures of the teeth such as the gingiva and the periodontal ligament. In the gnathic region, it is usually presents as an asymptomatic slow growing lesion, but occasionally can present with a locally aggressive behavior.[3] Fibromyxomas are fairly indistinguishable from myxomas, as they both exhibit a proliferation of primitive mesenchymal cells that produce an amorphous mucoid-rich intercellular matrix. In this article, we report a case of a fibromyxoma and will exhaustively review the clinical presentation, histological features, differential diagnoses, and management of this rare neoplasm.

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CASE REPORT

A 23-year-old female patient reported to our department with the chief complaint of a painless growth in the palatal aspect of the left upper back tooth region for the past 2 years. The growth was initially small but increased gradually to attain the present size over the past 3 months. Her medical history revealed allergy from pain killers. General physical examination showed a moderately built, nourished female with steady gait with satisfactory vital signs. Extraoral examination revealed nothing significant. Regional lymph nodes were not palpable.

Intraoral examination revealed the presence of a well-circumscribed, solitary, pale pink, and round to oval growth measuring about 1.5 cm × 1.0 cm over the palatal gingiva in relation to teeth 23 and 24 [Figure 1]. On palpation, the growth was soft to firm in consistency, non-tender, and non-pulsatile. The growth was pedunculated and attached to inter-proximal gingiva of the associated teeth which were found to be periodontally sound and non-carious. The overlying mucosa was smooth, non-ulcerated, and without any vascular prominence. I.O.P.A radiographic examination

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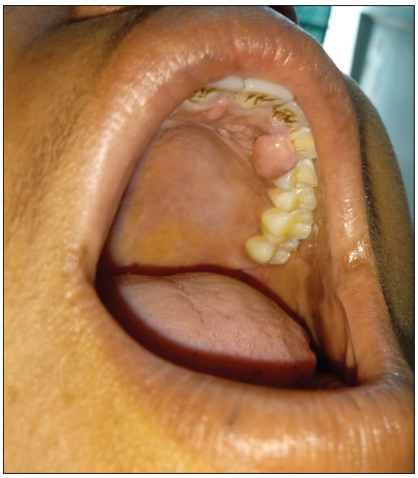

Figure 1: Clinical examination revealing the presence of a soft and round mass measuring about 7 mm in diameter on the left palate

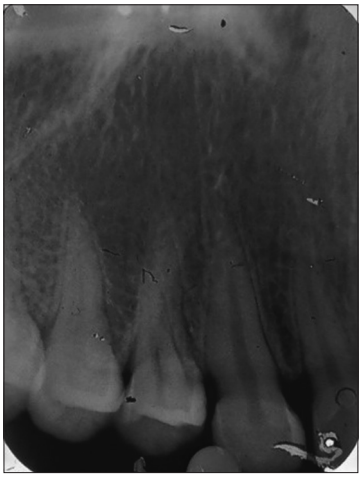

Figure 3: IOPA radiographic examination showed normal lamina dura of the involved teeth and no periapical pathology

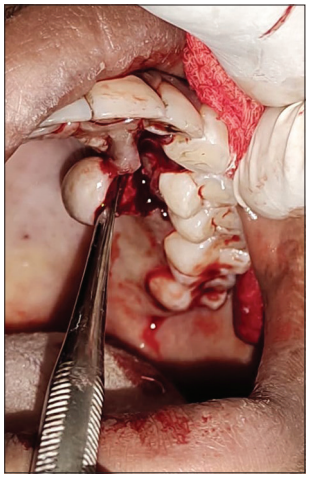

Figure 2: Excisional biopsy: Par operative procedure

showed normal lamina dura of the involved teeth without any periapical pathology [Figure 2].

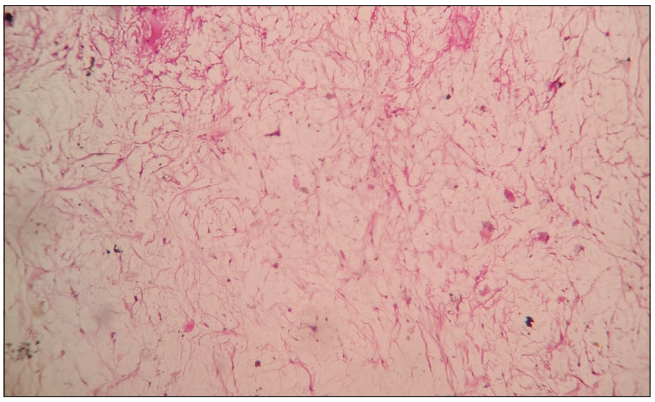

Figure 4: H&E stained Histological examination showing that the lesion was composed of loosely arranged hypocellular lesion composed of stellate and spindle shaped cells

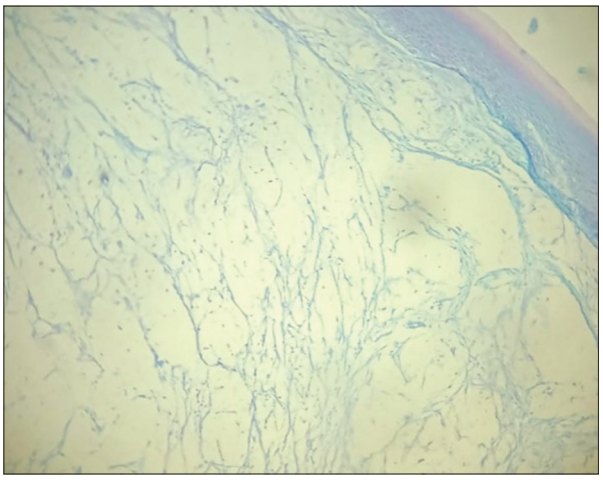

Figure 5: Alcian blue stained histological examination showing that mucoid mesenchymatous stroma composed of hyaluronic acid and glycosaminoglycans

Based on the clinical examination and history given by the patient, the growth was thought to be a benign neoplasm and a provisional diagnosis of "fibro-epithelial polyp" was made. Other differential diagnoses included fibroma, traumatic neuroma, neurofibroma, schwannoma, fibrous histiocytoma, and granular cell tumor.

After through, physical examination of the patient was advised for a routine hemogram which was found to be within normal limits. A with a written informed consent from the patient, an excisional biopsy was performed under local anesthesia [Figure 3]. The gross specimen was well-circumscribed, pinkish white, and oval-shaped measuring about 15.0 mm × 10.0 mm × 8.0 mm in dimension. Cut surface was homogenous, white, firm without any evidence of hemorrhage, or necrosis.

Sections stained with hematoxylin and eosin revealed the presence of atrophic stratified squamous surface epithelium with relatively flattened rete-ridges. The connective tissue

is characterized by presence of fibrocollagenous stroma with a well-delineated area showing myxomatous changes and irregularly dispersed angular mesenchymal cells resembling myoblasts [Figure 4]. Endothelial cell clumps and non-specific minimal inflammatory cell infiltration could be noted. Based on the clinical and histological findings, a definitive diagnosis of "Fibromyxoma" was made. Additional standing was performed for identification of myxomatous tissue was Alcian blue at pH1.0 and pH 2.5 [Figure 5]. A follow-up of 6 months was done, no complication or episodes of recurrences were noted.

DISCUSSION

Fibromyxoma is classified as a specific type of myxoma with an increase in fibrous/myxoid tissue ratio than myxoma.[1] It is a large and heterogeneous group of lesions affecting any part of the body. Common sites of occurrence are skin or subcutaneous tissues, genitourinary tract, gastrointestinal tract or in organs such as liver, spleen, or even parotid gland.

Fibromyxoma consists 3–20% of all the orofacial tumors. Thus, the extraosseous variety accounts for 3–8% of all the orofacial fibromyxoma, making it more distinct.

The most frequent location is the palate (41%), followed by buccal mucosa (18.2%), lips (13.6%), gingiva (13.6%), floor of the mouth, and retromolar area (4.5%). The clinical features of oral soft-tissue myxoma are not pathognomonic; therefore, diagnosis can be established only after histopathologic examination of the surgical specimen. Clinically, most cases can be misdiagnosed as fibrous epulis, fibro epithelial polyp, fibroma, or tumor of a minor salivary gland.[4-6]

Histogenesis of fibromyxoma remains uncertain, so several theories have been proposed regarding its origin. One theory suggests that altered primitive fibroblast produces excess mucopolysaccharides. Another theory postulates that fibromyxomas originate from remnants of embryonal mesenchyme. According to other researchers, it develops from degenerative changes in common fibromas; however, the difference in the sites of localized fibrous growths, as well as the presence of mast cells in areas of myxomatous degeneration, does not favor this theory. Finally, the latest theory by Brannon accepts that fibromyxoma is a true mesenchymal neoplasm.[7,8]

Histologically, fibromyxomas are hypocellular and mainly composed of spindle or stellate cells and reticulin fibers in abundant mucoid material. The randomly oriented stellate, spindle, or round cells have long, fine, anastomosing, and pale eosinophilic cytoplasmic processes. The cells are evenly dispersed in an abundant myxoid ground substance that characteristically contains a minimal amount of collagen fibers.[3,9] Mitotic figures were infrequent and tumors lack pleomorphism and necrosis. Paucity of blood vessels and absence of mast cells are also noted. The development of dense fibrous tissue between the myxomatous areas is a frequent finding, giving rise to the term myxofibroma.

Our case revealed the presence of connective tissue which is characterized by presence of fibrocollagenous stroma with a well-circumscribed central area showing myxomatous changes, with irregularly dispersed angular mesenchymal cells resembling myxoblasts and few nests of clumped endothelial cells. The mucoid mesenchymatous stroma is periodic-acid-Schiff negative but is stained positively with Alcian blue and reacts metachromatitally with Toluidine blue, properties that disappear when pretreatment with hyaluronidase is used. Myxoid or mucous stroma of soft tissue is composed of plentiful hyaluronic acid, which is non-sulfated glycosaminoglycans (GAGs), and sulfated GAG such as chondroitin sulfate. The ratio of hyaluronic acid to chondroitin sulfate is 4:1. However, non-sulfated GAG is difficult to be seen in H&E staining. Alcian blue staining (ABS) is performed for differential diagnosis. ABS (pH 1.0) demonstrates sulfated GAG and ABS (pH 2.5) shows alcinophilia in the tissues which contain hyaluronic acid or sialomucin.[10] Our histopathological examination of the section stained with ABS also revealed positive in pH 1.0 and stronger positive reaction at pH 2.5.

Differential diagnosis for myxoid appearing lesions in gnathic regions is odontogenic myxoma, oral focal mucinosis myxomatous degeneration in a fibrous lesion, and nerve sheath myxoma.

If the left untreated, fibromyxoma has unlimited growth potential; a phenomenon which distinguishes it from reactive non-neoplastic polypoid gingival growths. Fibromyxoma without bone destruction is treated with simple surgical excision, while those with bone destruction require excision and marginal curettage. Recurrence is usually due to insufficient removal of the tumor and lack of capsule. Therefore, the follow-up period of at least 6 month for 3 year, followed by self-observation is necessary to rule out intraosseous extension and recurrences. In our case, a follow-up of 6 months was done with no episodes of recurrences, which was noted.

CONCLUSION

Although this tumor is very rare, these are chiefly asymptomatic, osseous variants can be quite aggressive.

Thus, diligent histopathological examination is needed for proper diagnosis and necessary treatment.

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Case Report

A Rare Case of KMT2A Gene Mutation with Tall Stature and Acute Myeloid Leukemia

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Abstract

Lysine methyltransferase 2A (KMT2A) gene mutation is an extremely rare mutation of chromosome 11. It is usually associated with Wiedemann–Steiner syndrome or acute myeloblastic leukemia and commonly inherited as an autosomal dominant trait. The KMT2A gene-encoded lysine methyltransferase plays an essential role in regulating gene expression during early development and hematopoiesis. Clinical features of Weidemann–Steiner syndrome are variable and include facial dysmorphism (thick eyebrows, flat nasal bridge, and hypertelorism), intellectual disability, short stature, hypertrichosis cubiti, and hypotonia. Phenotypically, Wiedemann–Steiner syndrome is similar to Cornelia de Lange syndrome. However, genetic mutation of the KMT2A gene helps to differentiate the two conditions. Here, we present a 15-year-old boy, second born to a non-consanguineously married couple, who presented with facial dysmorphism (thick arched eyebrows, thick lips, low set ears, and flat nasal bridge), tall stature, global developmental delay, attention deficit hyperactive disease, and bleeding manifestations. Clinical and laboratory evaluation was suggestive of leukemia. Genetic testing revealed KMT2A gene mutation.

Key words: Acute myeloid leukemia, Facial dysmorphism, Lysine methyltransferase 2A gene mutation, Mixed lineage leukemia, Wiedemann–Steiner syndrome

INTRODUCTION

Lysine methyltransferase 2A (KMT2A) gene or mixed lineage leukemia (MLL) gene is a protein coding gene. This gene is important in regulating gene expression during early development and hematopoiesis. It regulates the expression of multiple genes including the homeobox (HOX) gene. Recurrent translocations in leukemia usually involve MLL. They can be either acute lymphoblastic leukemia or acute myeloblastic leukemia (AML). Such leukemias involving the MLL have unique clinical and biological characteristics with poor prognosis.

KMT2A gene mutation is also associated with many syndromes and most frequently encountered is the Wiedemann–Steiner syndrome. This was first reported in the year 1989 by Wiedemann Steiner *et al.* as an Autosomal Dominant condition. It's commonly referred to as the "hairy elbow syndrome" due to the presence of hypertrichosis cubiti, but this was not found in all the cases.[1,2] The clinical features of this condition are vivid with no gender predilection. The commonly seen phenotypic variants are – hypertelorism, flat nasal bridge, long philtrum, thick-arched eyebrows, short stature, hypertrichosis cubiti, developmental disorders like-intellectual disability (ID), learning disabilities, attention deficit hyperactive disease (ADHD), and autism spectrum disorders. These neurodevelopmental manifestations can range in severity from mild disease to profound delays.

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CASE REPORT

A 15-year-old boy, 2nd born to a non-consanguineously married couple, born at term gestation with history of perinatal depression requiring newborn intensive care unit care for 4–5 days with global developmental delay, ID, and ADHD was brought with complaints of spontaneous bleeding from

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the gums and skin. On examination, he was found to have facial dysmorphism [Figure 1a] in the form of-thick arched eyebrows, thick lips, depressed nasal bridge, hypertelorism, low set ears with microtia, and an absent external acoustic canal of the left ear [Figure 1b]. He had tall stature with height of 181cm (>97th centile on the combined WHO and IAP growth charts) [Figure 2], but clinical signs for marfanoid habitus was negative, i.e., Wrist sign and Thumb sign [Figure 3]. He was pale and had petechiae over the extremities. Hence, considering the possibility of leukemia, he was evaluated. Complete hemogram showed leukocytosis (16,610 cells/cu mm). Peripheral blood smear showed lymphocytosis (42%) with 6% blast cells and thrombocytopenia (15,000 cells/cu mm). Bone marrow aspiration and biopsy were suggestive of Acute Myeloid Leukemia with basophilia.

Figure 1: (a) Depicting the facial dysmorphism, and (b) depicting left ear microtia with absent external acoustic canal

Figure 2: This figure depicts the tall stature seen in our case

Karyotyping revealed: 47, XY, + mar [4]/47, XY, t (?: q23.3), mar [15]/46, XY [1].

Fluorescent *in situ* hybridization revealed: KMT2A (MLL) translocation: t (v; 11) (?; q23) [Figure 4].

The next-generation sequencing panel revealed national rental affordability scheme (NRAS) and STAG 2 gene mutations. Hence, a diagnosis of AML with MLL and NRAS/STAG-2 mutation was made. Phenotypically, this boy exhibited features of Wiedemann–Steiner Syndrome, but tall stature was an exception. He was initially treated with induction chemotherapy with Daunorubicin and cytarabine – 3+7 cycles at the end of which he had minimal residual disease (MRD), that is, MLL analysis of 1%, which was treated with high dose cytarabine. Following this regimen, he was free of MRD and bone marrow transplant (BMT) was done with a full HLA matched sibling. Despite the poor prognosis associated with KMT2A gene mutation and AML, the child is currently doing well after BMT.

DISCUSSION

Wiedemann–Steiner syndrome (WDSTS) associated with KMT2A gene mutation is an exceptionally rare autosomal dominant syndrome with a prevalence of <1 in 1,000,000.[3]

In 2012, Jones *et al.*[4] identified the haploinsufficiency of the gene KMT2A (MLL) as the genetic cause of WDSTS. Whole-exome sequencing was performed in six patients with a suggestive phenotype (hypertrichosis cubiti, short stature, ID, and facial features consistent with the patients reported by Wiedemann and Steiner) and detected de novo loss-of-function mutations in five of the six patients. KMT2A encodes a DNA-binding protein that methylates a lysine residue on histone H3 lysine K4 (H3K4). It consists of 37 exons, but a major transcript of 14982 bp produces a 3969 amino acids protein from 36 of the 37 exons. The

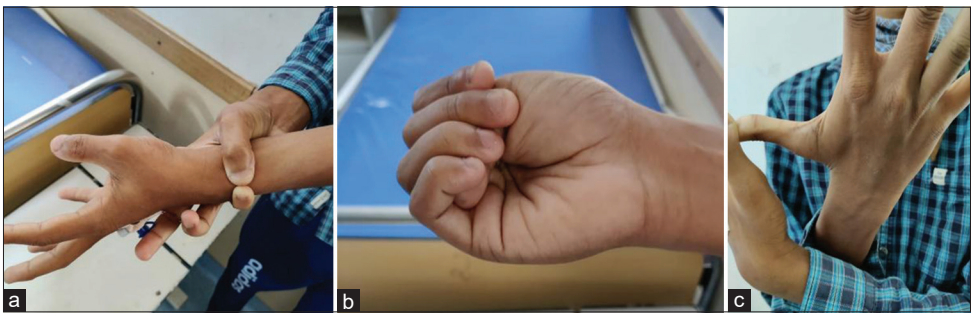

Figure 3: (a-c) Negative clinical signs of marfanoid habitus

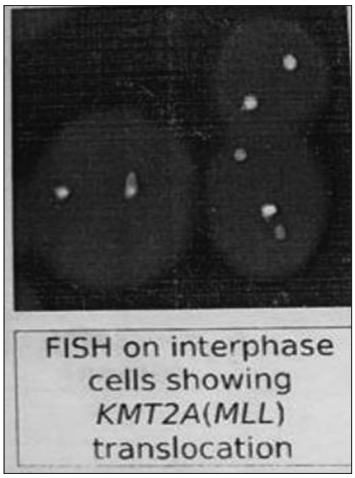

Figure 4: Fluorescent *in situ* hybridization showing mixed lineage leukemia translocation

protein contains several functional domains, including the SET domain, responsible for its H3K4 methyltransferase activity.[5] As discussed above, histone methyltransferases act as "writers." KMT2A, indeed, positively regulates the expression of many target genes, including genes belonging to the HOX complex and other genes involved in embryonic development.[6-8] Studies on mice also demonstrated that KMT2A is highly expressed in adult hippocampal neurons and is critical for synaptic plasticity, cognition, complex behaviors, and long-term memory.[9,10] Other members of the family of H3K4 methyltransferases are associated with other chromatinopathies, ex-KMT2D and KMT2B are associated with Kabuki syndrome and Kleefstra syndrome, respectively.

A French study[2] of 33 cases of Weidemann–Steiner syndrome observed a broad phenotypic spectrum with regard to ID (mild to severe), the facies (typical or not of WSS) and associated malformations (bone, cerebral, renal, cardiac, and ophthalmological anomalies). Hypertrichosis cubiti that was supposed to be pathognomonic in the literature was found only in 61% of their cases. This is the largest series of WSS cases yet described to date. A majority of patients exhibited suggestive features, but others were less characteristic, only identified by molecular diagnosis. The prevalence of WSS was higher than expected in patients with ID, suggesting that KMT2A is a major gene in ID.

In a study of Wiedemann–Steiner syndrome in monozygotic twins,[11] they identified a *de novo* mutation in KMT2A associated with psychomotor developmental delay, facial dysmorphism, short stature, hypertrichosis cubiti, and small kidneys. This finding in monozygotic twins gave specificity to the WSS. The article says that the description of more cases of WSS is needed for further delineation of this condition. Small kidneys with normal function have not been described in this condition in the medical literature before.

In our study, the child showed tall stature in association with KMT2A gene mutation which is a rare manifestation and was similar to a case reported in a study conducted by Lee *et al.*[5] This was a study conducted on two unrelated individuals who were diagnosed as atypical Wiedemann–Steiner syndrome, in which one of the children was found to have tall stature.

CONCLUSION

KMT2A gene mutation being rare has vivid phenotypical presentation. In our case, the boy has exhibited tall stature. Leukemia caused due to KMT2A gene mutation is usually associated with poor prognosis. The child is currently doing well and is on follow-up.

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Case Report

Drug-induced Oral Erythema Multiforme: Report of Two Cases with Review of Literature

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Abstract

Erythema multiforme (EM) is a blistering and ulcerative mucocutaneous disease which may have oral manifestations. It appears as a diagnostic dilemma because the oral cavity presents with varied appearances (multiforme means many forms). Infections (particularly herpes simplex virus) and various drugs seem to predispose toward development of EM. These may trigger an immunologic derangement that produces the disease. Drug-induced EM is a rare entity which accounts for <10% of all cases. Health-care providers must be careful regarding such adverse effects of the drugs. Here, we report two cases of oral EM in which drugs seem to be the precipitating factor, which warrants judicious use of such drug regimens and the importance of reporting and monitoring mechanisms for effective management.

Key words: Adverse drug reactions, Erythema multiforme, Mucocutaneous disorders, Vesiculobullous lesion

INTRODUCTION

Erythema multiforme (EM) is an acute, self-limiting, hypersensitive, and mucocutaneous lesion with varied etiology. It consists of a spectrum of disorders, including Erythema multiforme minor (EMm), Erythema multiforme major (EMM), Stevens Johnson syndrome (SJS), and Toxic epidermal necrolysis (TEN).[1,2]

EM appears as a consequence of allergic host response to antigenic challenge which is triggered primarily by antigens, induced commonly by exposure to microbes or drugs. Although the exact pathogenesis is unknown, there is a tendency to consider both EMm and EMM as part of one spectrum that is most often triggered by viral infections, and SJS and TEN as a separate spectrum most often elicited by drugs. All variants of EM typically show some degree of cutaneous involvement. EMm characteristically affects single mucosa and may be associated with symmetrical target skin lesions on the extremities. EMM typically involves two or more mucous membranes with more variable skin involvement. The severe variants SJS and TEN usually involve the skin extensively.[2]

Oral EM is a distinct but less well recognized variant of EM, introduced by Kennett in 1968.[3,4] It has been reported that primary attacks of oral EM are confined to oral mucosa without skin involvement. Subsequent attacks can produce more severe form of EM involving the skin.[1] Drug-associated EM is relatively uncommon and reported to be <10%.[1] Although a variety of drugs has been associated with EM, antibiotics and analgesics are most commonly implicated.[2-5]

Here, we present two case reports of drug-induced oral EM associated with intake of Fluoroquinolones and Nitroimidazole groups of antibiotics. The etiology, pathogenesis, diagnostic criteria, differential diagnoses, and treatment have been discussed in detail. The purpose of the article is to enlighten and empower the health-care providers so as to enable them to identify and manage such cases of drug-induced oral EM.

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CASE REPORT

Case 1

A 62-year-old female patient from semi-urban area reported to Department of Oral Pathology with chief complaint of burning sensation and pain in mouth due to ulcers for the past 10 days. After careful and thorough history taking, it was revealed that the patient had an episode of stomach upset approximately 10–12 days ago for which she took over the counter tablet of Norfloxacin and Tinidazole combination as self-medication. Subsequently, she developed blisters on her lower lip and cheeks next day. The blisters later transformed into extensive and irregular ulcerations in the mouth. She visited the local physician who prescribed chlorhexidine gel, but symptoms did not subside. Then she was referred to higher center.

Extraoral examination revealed ulcerations of both upper and lower lips showing cracking and fissuring with blood encrustation. Intraoral examination showed extensive and irregular ulcerations covered with yellowish-white slough surrounded by erythematous border on the upper and lower labial mucosa. Similar ulcerations were also present on the buccal mucosa bilaterally near the angle of mouth. [Figure 1] There was no involvement of the masticatory mucosa. On palpation, the ulcers were tender and bleeding was elicited on slightest provocation. The sudden onset and positive drug history along with above mentioned features were suggestive of oral EM. In this case, norfloxacin and tinidazole were the causative drugs for the lesion.

Patient was advised to discontinue the medications and was treated with systemic corticosteroid (Tab Prednisone 20 mg BID), levocetrizine 5 mg OD, topical anesthetic gel for 5 days. As the lesions were regressed clinically after 5 days, systemic steroids were tapered by 10 mg/day for a week to a maintenance dose of 5 mg/day for the next 1 week. The lesions completely regressed in 15 days. [Figure 2] No recurrence was noted over a follow-up of 6 months.

Case 2

A 46-year-old male patient from rural area reported to the outpatient department with chief complaint of mouth ulcers and difficulty in eating and drinking for the past 1 week. History revealed sudden onset of ulcers on his tongue and cheek 7 days back, which increased gradually in size. The patient visited physician for which he was prescribed multivitamins and topical steroids for local application.

After thorough questioning, the patient recalled that he had taken some over the counter medications of ofloxacin and ornidazole combination for loose motion almost 7 days back. The symptoms appeared from the next day of taking medication. Intraoral examination revealed a large bullae measuring about 1. 5 × 1. 2 cm in dimension involving the ventral surface of tongue and floor of mouth, covered with pseudomembrane, surrounded by erythematous halo and irregular borders. Erythematous areas were also noted on the left buccal mucosa and posterior palatal region in respect of 25, 26, and 27. [Figure 3] Nikolsky's sign was negative. Positive association of drug history and appearance of lesion along with the clinical features were suggestive of oral EM. Ofloxacin and ornidazole were the causative drugs in this case.

Patient was treated with systemic corticosteroid (Tab Prednisone 20 mg BID for 5 days which was tapered

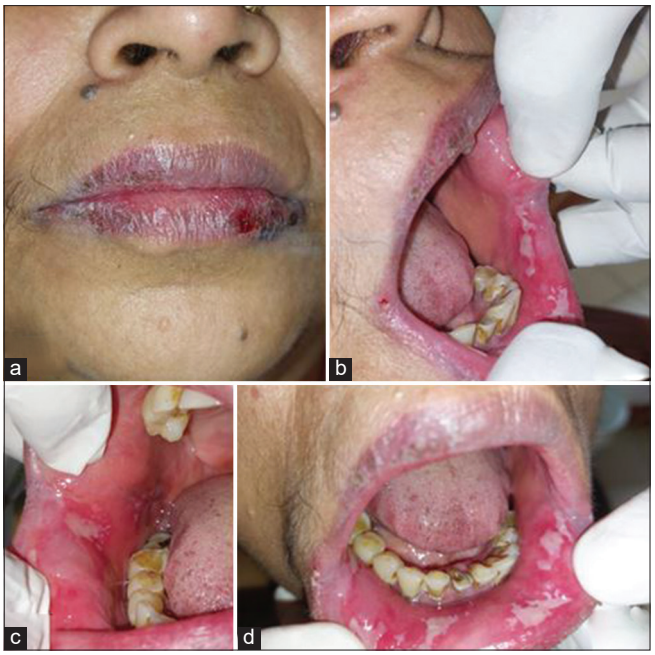

Figure 1: Composite image depicting encrustation on lips (a), irregular ulceration covered with pseudomembrane on buccal mucosa (b and c), and labial mucosa (d)

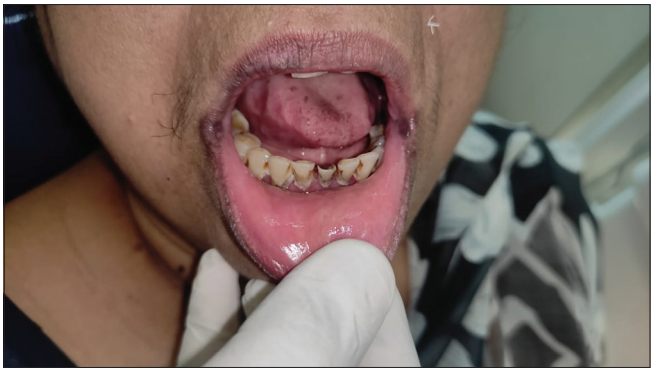

Figure 2: Photograph showing complete regression of the lesions after the treatment

gradually upto a maintenance dose of 5 mg/day), levocetrizine 5 mg OD, and topical anesthetic gel. Mouth rinse with Sucralfate suspension was advocated to promote healing of ulcer and alleviate the symptoms. Complete regression of lesion was seen after 10 days. [Figure 4] The patient is currently under review with no recurrence till date.

DISCUSSION

EM was first described by Von Hebra in 1866 as a relatively benign condition characterized by skin lesions with concentric color alterations. These lesions may have a variety of appearances including vividly erythematous discrete macules, papules, or occasionally vesicles and bullae (multiforme means many forms).[6,7] Stevens and Johnson in 1922 reported the severe form of EM with involvement of oral and conjunctival mucous membrane along with skin lesions. In 1950, Thomas suggested that EM and SJS were variants of the same pathologic process. In 1956, Lyell reported a series of patients with a life-threatening, rapidly evolving mucocutaneous reaction characterized by widespread erythema, necrosis, and bullous detachment of the epidermis resembling scalding, a condition currently known as TEN. In 1968, Kennett described an inflammatory oral disorder with lesions typical of the oral lesions of EM as "EM affecting the oral cavity"[4] [Table 1].

EM is a reactive mucocutaneous disorder. The exact pathogenesis of EM is unknown. Numerous factors such as microbial infection, drugs, food additives, malignancy, auto-immunity, radiation, immunization, and stress have been implicated to its development.[8] Herpes virus infection is considered to be involved in more than 90% of cases. Drug-associated EM is rare and reported to be <10%[1] of which most commonly implicated are antibiotics and analgesics. Very few cases of EM have been reported with the ingestion of Fluoroquinolones and Nitroimidazole groups of drugs. In our cases, manifestation of the lesion appeared after intake of these drugs. Patient was neither exposed to any kind of infection nor was allergic to any food additives. Hence, with this temporal occurrence of drug intake and appearance of the lesion, it was considered that etiological agent was drug (ofloxacin-ornidazole and norfloxacin-tinidazole) in our patients.

EM seems to result from a T-cell-mediated immune reaction to the precipitating agent, which leads to a cytotoxic immunological attack on keratinocytes that express non-self-antigens, with subsequent sub-epithelial and intraepithelial vesiculation; this leads to widespread blistering and erosions. In drug-induced EM, the reactive drug metabolites trigger the disease, and tumor necrosis factor alpha, released from keratinocytes, macrophages,

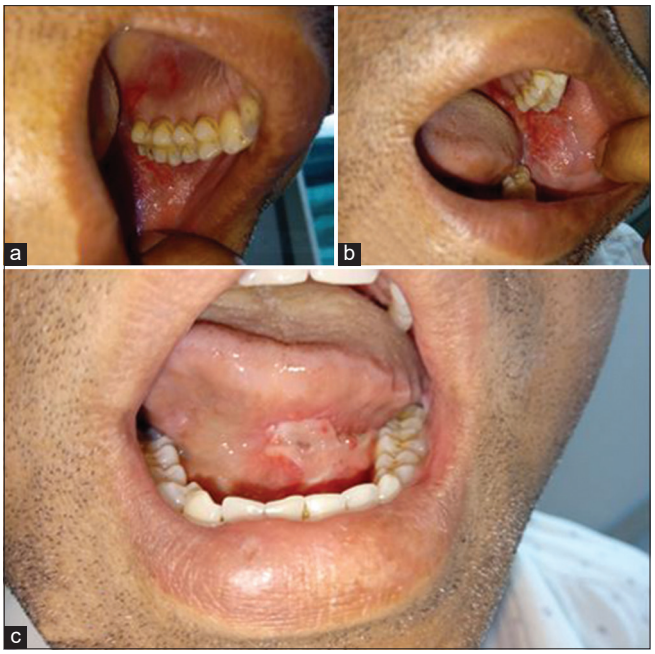

Figure 3: Composite image depicting erythematous areas in posterior palate on the left side (a), and irregular ulcerated areas in the left buccal mucosa (b), and bullae formation in floor of mouth (c)

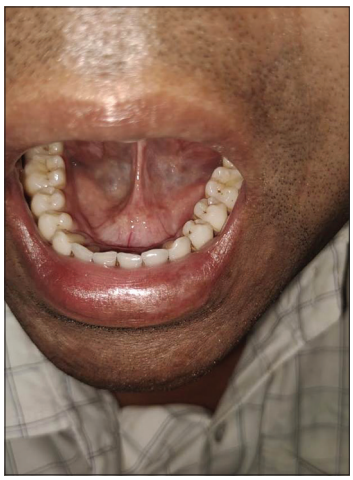

Figure 4: Photograph showing complete regression of the lesions

Table 1: Classification of the spectrum of erythema multiforme[4]

Variant	Author	Year of reporting
Erythema multiforme minor	Hebra	1866
Erythema multiforme major	Thomas	1950
Stevens Johnson syndrome	Stevens and Johnson	1922
Toxic epidermal necrolysis	Lyell	1956
Oral erythema multiforme	Kennett	1968

and monocytes, induces keratinocyte apoptosis causing the tissue damage.[2,3,8] Drug metabolism is altered and directed toward cytochrome P450 – metabolite pathway resulting in production of reactive and toxic metabolites.[1] Tissue damage is mainly due to apoptosis and not by inflammatory response. In addition to a cellular immune response, humoral immune mechanisms may be involved in the pathogenesis.[3]

The presentation of EM ranges from a self-limited, mild, and exanthematous variant with minimal oral involvement (EMM) to a progressive, fulminating, and severe variant with extensive mucocutaneous epithelial necrosis (SJS and TEN). Symmetrically distributed typical cutaneous target lesions and/or atypical raised target lesions are the hallmark.[5] Oral involvement is seen in some 70% of patients with EM.[2] Lips tend to become swollen and cracked, with bleeding and later crusting. Intraoral lesions appear typically on the non-keratinised mucosa and are most pronounced in the anterior parts of the mouth,[2] which were present in our cases too. The lips, labial mucosa, buccal mucosa, tongue, floor of mouth, and soft palate are the most common sites of involvement. Usually, the gingiva and hard palate are spared.[7]

There is no specific diagnostic test for EM. Biopsies are advised only in the early vesicular lesions and not in the ulcerated ones as histopathologic appearances are non-specific.[3] Diagnosis of EM usually entails excluding other similar diseases by careful review of the clinical history and detailed clinical examination.[8] Features more suggestive of EM are the acute onset (or recurrent nature), oral lesions appearing on the lip and anteriorly in the mouth, and pleomorphic cutaneous lesions (typical and atypical target lesions).

Drug-induced oral EM needs to be primarily differentiated from fixed drug eruptions (FDE). FDE is a type of drug reaction which is characterized by recurrence of lesion at the same site on repeated exposure to the drugs. It usually occurs within 30 min to 8 h after the drug is taken.[9] The confirmatory test is an oral challenge test. The most common site of involvement is skin and glans penis.[9] Isolated involvement of oral mucosa is rare and any intraoral site including hard palate may be involved in FDE. Whereas, lining mucosa in the anterior part of the mouth is typically affected in oral EM sparing the hard palate and gingiva.[7] Furthermore, primary attacks of oral EM are confined to oral mucosa without skin involvement.[1] The patients in our cases did not give any history of similar recurrent lesions with such drugs on any previous occasion. Other differential diagnoses to be considered in the lesions confined to oral cavity are herpes infection, vesicullobullous lesions such as pemphigus, pemphigoid, and erosive LP. Herpetic lesions are usually smaller, well circumscribed, more common in lips, and keratinized mucosa especially the gingiva and hard palate; and almost always invariably preceded by prodromal symptoms. Our cases had no gingival lesion or prodromal symptoms. The lesions were large and irregular. Temporal relationship between the drug intake and onset of disease excludes the possibility of vesiculobullous lesions such as pemphigus or pemphigoid. Nickolsky's sign was also absent in our cases. Lichen planus may show similar ulcerations accompanied with Wickham's straie, which were absent in our cases.[1,3]

Drugs are double edged sword, which gives beneficial results and can also cause adverse reaction in certain conditions. Adverse drug reaction (ADR) can manifest in many forms such as erythema multiforme, fixed drug eruption, and anaphylactic reactions.[1] Very few cases have been reported as EM associated with Fluoroquinolones and Nitroimidazole groups of drugs. After extensive literature search, the list of the reported cases is summarized in Table 2. The fluoroquinolones (ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, etc.) are a family of broad spectrum, systemic antibacterial agents that have been used widely as therapy of respiratory, urinary tract, and G.I.T. infections. They are active against a wide range of aerobic Gram-positive and Gram-negative organisms.[10] On the other hand, Nitroimidazole antibiotics (Metronidazole, Ornidazole, Tinidazole, etc) have been used against anaerobic bacterial and protozoal infections.[10] In India, these drugs are among the most common drugs self-medicated by general population for any gastrointestinal infections. Furthermore, both these groups of drugs are used extensively by Dental Surgeons for management of oral and dental infections, both pre and postoperatively, due to coverage of aerobic and anaerobic micro-organisms and potency against the infective oral microflora in dental infections. Therefore, health-care providers must be cautious before prescribing such drugs and should be aware of their adverse effects.

The management of EM can be challenging. Triggering agent must be identified and withdrawn immediately. Corticosteroids are the most commonly used drugs in the management of EM.[1-3,5] Second-line therapies are generally reserved for refractory cases and include alternate immunosuppressive agents and antimicrobial medications.[11] In our cases, both patients responded very well with the systemic prednisolone therapy along with symptomatic management of erosions and ulcers. They were also sensitized and cautioned about the offending drugs.

Table 2: Case reports showing EM with Fluoroquinolones and/or Nitroimidazole group

Author	Age	Sex	Site of involvement	Diagnosis	Suspected Drug	Drug taken for	Duration of onset of symptoms after taking drug	Treatment given
Singbal and Rataboli (2005)[12]	30	Male	Skin, oral mucosa	EM, SJS	Tinidazole	Diarrhoea	02 days	Not available
Mazumdar and Shome (2012)[13]	50	Male	Lips, oral mucosa, skin	SJS	Metronidazole	Erosive LP	06 h	Systemic steroids
Deore *et al*. (2014)[14]	21	Female	Skin, conjunctiva, oral mucosa	SJS	Ciprofloxacin, Tinidazole, Diclofenac	Dental pain	03 days	Systemic steroids
Bhusan (2015)[15]	Not available	Not available	Oral, genital mucosa, skin	SJS	Tinidazole	Not available	01 h	Not available
Narasimhamurthy *et al*. (2015)[16]	39	Male	Skin	EM Skin	Ciprofloxacin, Metronidazole	Road Traffic Accident	01 day	Systemic steroids and Anti- histaminics
Chandak *et al*. (2020)[17]	27	Male	Lips	EM oral	Ofloxacin, Ornidazole	Loose motion	03 days	Topical steroids and Anti- histaminics
Aschalew *et al*. (2020)[18]	22	Female	Lips, vagina, skin	EM Oral and Skin	Ciprofloxacin	Typhoid fever	03 h	Systemic steroids and Anti- histaminics

CONCLUSION

Drug-induced oral EM is uncommon and needs to be differentiated from other oral ulcerative lesions for effective management. Detailed history taking and clinical examination are of utmost importance for early diagnosis. It is important for the health-care providers to report such cases to create awareness among general population and sensitize them regarding judicious use of drugs, as majority of them go unreported due to lack of knowledge of the patients and self-medication causing serious ADR in them. A robust ADR monitoring system with a feedback mechanism and awareness of the prescribers and patients can help prevent, identify, and manage such conditions much more effectively.

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Case Report

Left Pulmonary Agenesis with Congenital Diaphragmatic Hernia: A Rare Congenital Anomaly

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Abstract

Complete absence or severe hypoplasia of one or both lungs is termed as pulmonary agenesis. It is a congenital disorder with a prenatal autopsy incidence of 1 in 15000, though true incidence is still unknown. Unilateral pulmonary involvement is more common than bilateral pulmonary agenesis. The anomaly may affect either lung, with more predilections for the right side. We observed a case of the left lung agenesis with congenital left sided diaphragmatic hernia and to the best of our knowledge very few cases have been reported in the previous literature.

Key words: Diaphragmatic hernia, Lung agenesis, Multidetector CT angiogram

INTRODUCTION

Lung agenesis is an extremely rare congenital anomaly of the lung. Proper knowledge and early diagnosis of the condition are a must to avoid management as effusion, collapse, or consolidation. Contrast-enhanced computed tomography (CECT) is the most effective diagnostic tool to differentiate various mimics and assess airways and vascular structures.

CASE REPORT

An 8-year-old boy from Sitapur presented to Pediatric outpatient clinic of King George Medical University with complaints of recurrent chest infections. He was born to a 36-year-old second gravida mother with non-consanguineous marriage at term gestation with no perinatal complications. Developmental milestones were normal for age.

On physical examination, patient was active, alert with normal anthropometric parameters. He had tachycardia (heart rate-110/min), tachypnea (respiratory rate-60/min) with mild subcostal recession. His chest was normal shaped, with slightly decreased movements on the left side. Trachea was central in position. There was dull percussion note on the whole of the left side of chest. Breath sounds were reduced on the left side. Per abdominally, liver was palpated on the right side, 1 cm below costal margin. On echocardiography cardiologist could not be able to localize pulmonary arteries properly so he suggested CT pulmonary angiography.

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Investigations

A CT chest in pulmonary angio protocol [Figures 1-5] was performed for better evaluation. The CT showed complete opacification of the left hemithorax on the topogram with no mediastinal shift. These findings were confirmed on lung and soft-tissue window. Reconstructed and raw images confirmed complete absence of the left lung. Small left bronchial stump was present with abrupt cutoff. The pulmonary artery (PA) and veins were completely absent on the left side. Left upper abdominal viscera including stomach, spleen, and omentum were herniated into the left to occupy entire left hemithorax space. There was mild compensatory hyperinflation of the right lung. There was also dextroscoliosis with segmentation anomaly of the upper dorsal vertebrae. These findings confirmed a diagnosis of the left pulmonary agenesis type I with the left-sided diaphragmatic hernia.

Treatment

No treatment is required in asymptomatic cases.[1] Treatment is necessary for lower respiratory tract infections.

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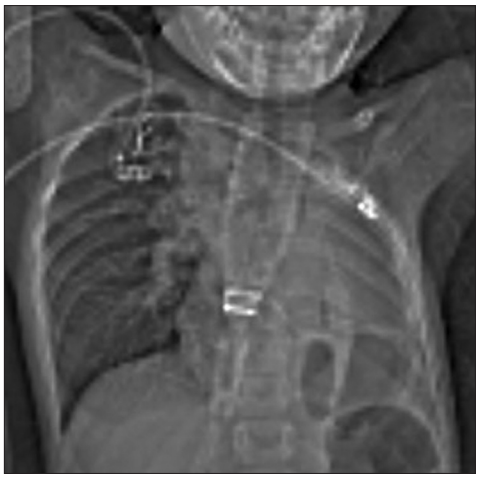

Figure 1: Computed tomography scanogram of the chest showing complete opacification of the left hemithorax with cranial migration of abdominal contents into the thorax the left airway is not present

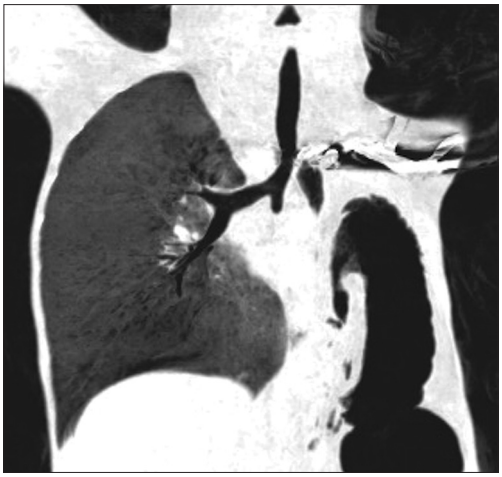

Figure 2: Coronal MnIP image - shows short left bronchus stump with complete cut-off and absent left lung, trachea, and Rt bronchus normal

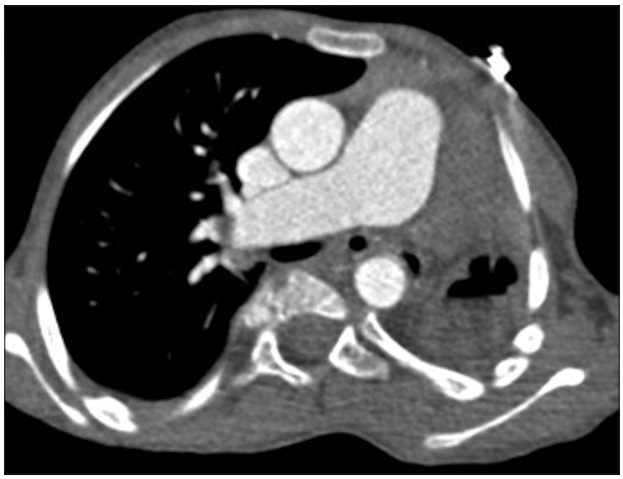

Figure 3: Axial thin images of computed tomography chest at the level of the pulmonary artery (PA) and heart show absent left PA with dilated right and main PA

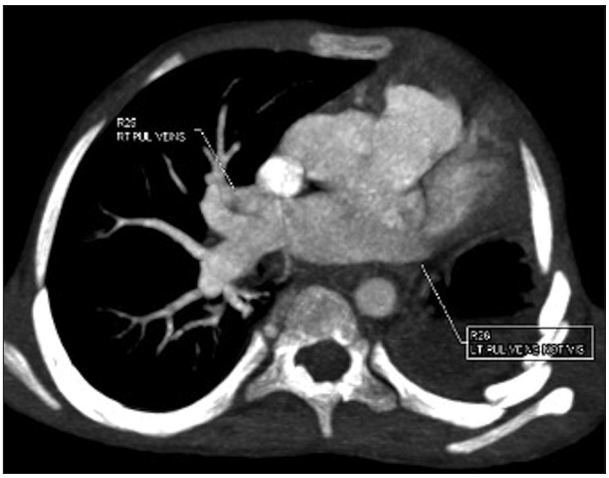

Figure 4: The axial image at the level of the heart shows cardiac chambers and absent left pulmonary veins. The left lung is absent with abdominal content of the left side herniated into the thorax

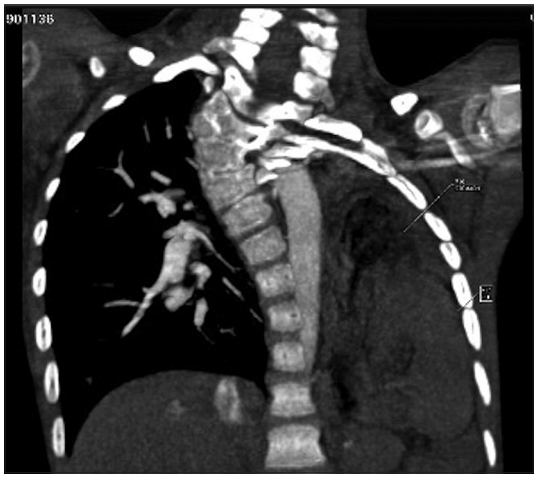

Figure 5: Coronal thin image of computed tomography chest posterior to heart shows absent left lung. The stomach and spleen are occupying the space in the left hemithorax. There is also dextroscoliosis

Patients having stumps may require surgical removal of the stump if postural drainage and antibiotics fail to resolve the infection.[2] Corrective surgery of associated congenital anomalies, wherever feasible, may be undertaken.[3]

Outcome and Follow-up

Prognosis depends on two factors. First, the severity of associated congenital anomalies and second, involvement of the normal lung in any disease process.[3] Patients with the right lung agenesis have a higher mortality than those with the left lung agenesis because of compression of the tracheobronchial tree by the shifting of normally midthoracic structures into the right chest.[4] If patient survives the first 5 years without major infection, an almost normal life span can be expected.[5] The patient was managed conservatively. The clinical symptoms were improved and the right lung was normal with no other associated congenital anomalies;

therefore, no surgical intervention was performed. The patient was followed at hospital out-patient department for a year and was clinically well.

DISCUSSION

Pulmonary agenesis and aplasia are rare abnormalities with reported incidence between 0.0034% and 0.0097%.[6] Many cases of pulmonary agenesis, aplasia, and hypoplasia have been reported at different ages including prenatally in new-born, infants, children, adults, and even at 90 years of age.[4,7-9] Bilateral pulmonary agenesis is a rare congenital anomaly that may occur in anencephalic babies.[1] Unilateral agenesis, aplasia, and hypoplasia are comparatively more common. These may have fewer symptoms and non-specific findings, that is, why only one-third cases are diagnosed during the lifetime. Functionally, unilateral agenesis and aplasia are similar. The sole lung is larger than normal, and this enlargement is true hypertrophy and not emphysema.[1]

Failure of development from the foregut can lead to these types of congenital pulmonary malformations. Bilateral pulmonary agenesis is caused by developmental arrest at the stage of the primitive lung bud. The respiratory anlage at a later stage may develop only unilaterally and leads to unilateral lung agenesis. Lobar agenesis results when developmental arrest on one side occurs in an older embryo; however, pulmonary hypoplasia may occur during the last trimester of pregnancy with failure of final alveolar differentiation.[1]

Genetic, teratogenic, and mechanical factors may have a bearing on etiology.[4,10] These are generally sporadic, with nearly similar occurrence in both the sexes and involve both lungs equally.[4,7] Only few cases are reported in siblings in an autosomal recessive pattern.[1] There is high incidence (>50.0%) of associated cardiac, gastrointestinal, genitourinary, skeletal, central nervous system malformations, and VACTERL sequence.[1,4,10,11]

Schneider and Schawatbe initially classified pulmonary agenesis which was later modified by Boyden into three types according to stages of development of lung bud:[12]

1. Type I: Absence of lung parenchyma, bronchus, and blood supply to affected side (Agenesis).
2. Type II: Absence of lung parenchyma with the presence of rudimentary bronchus only (Aplasia).
3. Type III: Variable amount of lung parenchyma, bronchial tree, and vasculature (Hypoplasia).

As this anomaly can occur at any age, the possibility of lung agenesis should be in differential diagnosis of patients having decrease to absent breath sounds with less or no movement of unilateral chest wall and opaque hemithorax in plain film. For confirmation, diagnostic imaging such as chest computed tomography scan, magnetic resource imaging, bronchoscopy, and chest angiography can be done. The early detection of the pulmonary agenesis is essential to reduce the development of fibrosis in patient's unilateral lung which can occur as result of recurrent chest infection. The surgical procedures should also be in consideration in the presence of other congenital anomalies or complications.[13]

LEARNING POINTS/TAKE HOME MESSAGES/CONCLUSION

Lung agenesis is an extremely rare congenital broncho-pulmonary anomaly.

- CECT is the most effective diagnostic tool to differentiate various radiographic mimics (like effusion, collapse, or consolidation) and assess airways and vascular structures.
- Proper knowledge and early diagnosis of the condition are a must for early diagnosis and timely definitive management.

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Review Article

Hydroxyzine for the Management of Pruritus

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Abstract

Pruritus is an unpleasant sensation on skin that can be observed in many patients attending dermatology clinic. Chemical mediators such as histamine, serotonin, acetylcholine, and prostaglandins are involved in itch. Itch is generally classified into several types such as cutaneous, neuropathic, neurogenic, and psychogenic itch. Hydroxyzine is the first generation anti-histamine used in pruritus treatment. It is also been used in treatment of other disease conditions such as dermatoses, generalized anxiety disorder, and tension caused by psychoneurosis. It is a potent inverse agonist of H1 receptors that inhibits the histamine release from mast cells. Onset of action occurs between 15 and 60 minutes and duration of action is 4-6 hours. This work discusses the role of hydroxyzine in pruritus management and clinical expertise of different physicians on hydroxyzine use in pruritus patients.

Key words: Anti-histamines, Pruritus, Histamine, Hydroxyzine

INTRODUCTION

Pruritus or itch is an unpleasant sensation on skin that evokes scratch. It is a common condition encountered by physicians in many patients attending hospitals especially dermatological wards. More than a disease, it is considered as a benign symptom.[1]

CLASSIFICATION OF ITCH

Itch is classified into the following types:[1]

- Cutaneous
- Neuropathic
- Neurogenic
- Psychogenic.

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CUTANEOUS ITCH

It is also called as pruritoceptive itch and is due to the result of inflamed skin

NEUROGENIC ITCH

It originates centrally without any evidence of neuronal pathway. This kind of itch is reported in patients with cholestasis.

NEUROPATHIC ITCH

It originates centrally along afferent nerve pathway and as a result of damage to the nervous system.

PSYCHOGENIC

It is observed in patients with delusional conditions like parasitophobia.

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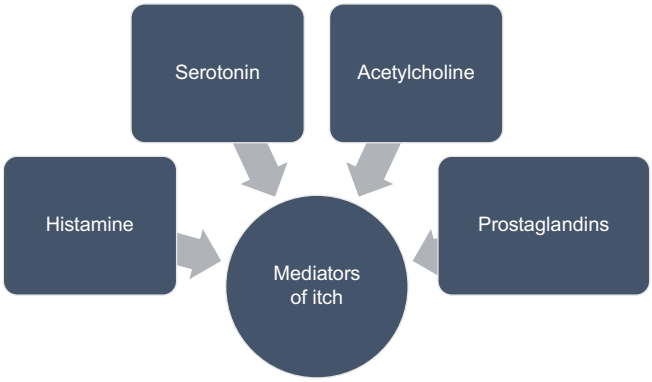


CHEMICAL MEDIATORS INVOLVED IN ITCH

Itch is a result of involvement of many pruritogenic substances and receptors. Common chemical mediators involved in pruritus are.[1]

HYDROXYZINE

It is a first generation anti-histamine used in treatment and management of pruritus. It exhibits sedative, anxiolytic, and antiemetic properties. It was first developed in 1995 and since then it is used commonly for the treatment of various allergic conditions such as pruritus, dermatoses, urticaria, and histamine-mediated pruritus. It is also used in treatment of other conditions like generalized anxiety disorder and tension caused by psychoneurosis. Its sedative properties likely to occur at the subcortical level of the central nervous system.[2]

The argument regarding utilization of first generation anti-histamines is still alive because of some other debates impelled by empirical experience. Thus, Allen Kaplan favored the use of high doses of hydroxyzine and diphenhydramine if second generation anti-histamines does not accomplish satisfactory symptom control in patients even in case of doubling doses. He supported his statements with compelling reasoning:[3]

- First generation anti-histamines can offer relatively lower specificity for H1 anti-histamine receptors and this may provide additional beneficial effects by other mechanisms such as anti-muscarinic, anti-adrenergic, anti-serotonin effects, and activity against H4 receptors.
- The use of first generation anti-histamines is limited because of sedation, somnolence, and performance impairment. However, unlike other conditions where histamine plays a crucial role, these features in urticaria patients are closely linked with the nature of the disease, as sleep deprivation because of nighttime itch can be the real underlying cause in them. Therefore, sedating antihistamines (AH) have a paradoxal positive effect on the state of alertness.
- The sedative effects are short lived and usually wear off by day 4 of the treatment with first generation AH.
- The alternative for sedation is prescribing corticosteroids and expensive drugs such as cyclosporine, methotrexate, sulfasalazine, intravenous gamma globulin, dapsone, hydroxychloroquine, colchicine, and cytoxan. However, these drugs have deleterious risks in the long-term.[3]

CONCEPT OF NEURONAL SENSITIZATION

Chronic itch is generally associated by allokinesis and hyperkinesis that are likely caused due to neuronal sensitization. This signifies the change in sensitivity of itch-processing neurons. Neuronal sensitization includes numerous factors acting at targets in the skin, spinal cord, and brain as represented in Figure 1.[4]

MECHANISM OF ACTION

H1 histamine receptors are responsible for initiation of hypersensitivity and allergic reactions. Whenever, a person is exposed to antigen this results in degranulation of mast cells and basophils with release of histamine. Histamine binds to H1 receptors and aggravates inflammatory activity further with the release of pro-inflammatory mediators such as interleukins.[2]

- Hydroxyzine is a potent inverse agonist of H1 receptors.
- It blocks the H1 receptors, dampens the receptor activity, and thus inhibits release of chemical mediator histamine from mast cells that is involved in pruritus.

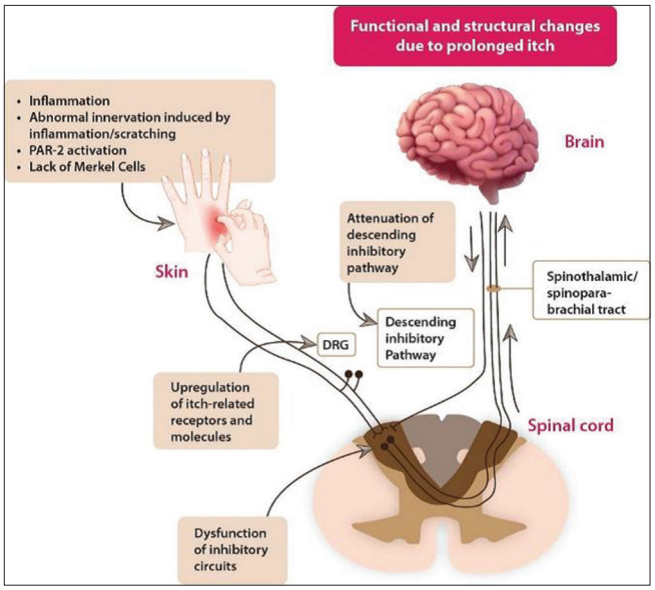
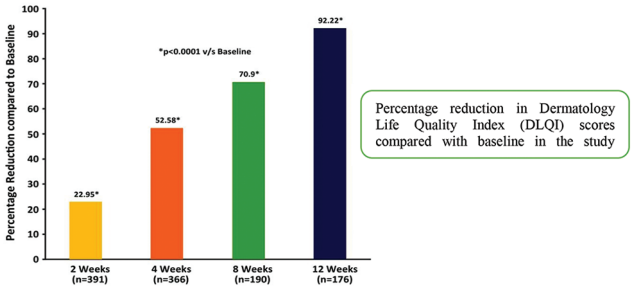


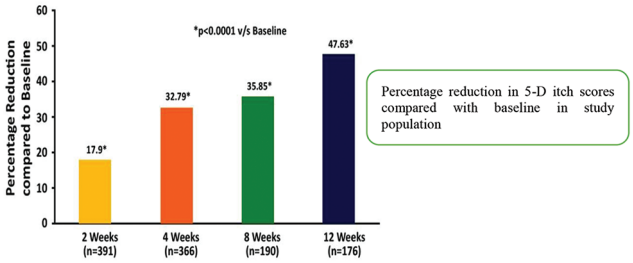
Figure 1: Neural sensitivity to pruritus. DRG: Dorsal root ganglion, PAR: Protease-activated receptor

- Its off-target activity allows to use this drug as a sedative anxiolytic.
- Its onset of action is very fast and occurs between 15 and 60 min and duration of action is 4–6 h.[2]

THERAPEUTIC EFFICACY OF HYDROXYZINE

Thomas *et al*. assessed the efficacy of hydroxyzine hydrochloride in chronic pruritus patients (n = 400). This study concluded that hydroxyzine hydrochloride significantly improved pruritus condition ($P < 0.0001$), quality of life in patients ($P < 0.0001$), and was well tolerated in patients with chronic pruritus at the end of 12 weeks treatment.[5]





- The European guidelines on chronic pruritus recommend use of hydroxyzine as a first choice in treatment of pruritus because of its antipruritic, anxiolytic, and sedative properties.[4]
- According to the Indian Consensus 2021, hydroxyzine is generally the first line of treatment for acute and chronic pruritus.[4]

Key Points

- Hydroxyzine helps to control pruritus condition, improves quality of life, and itch scores in patients.
- Therefore, hydroxyzine should be preferred as first line treatment option in patients with pruritus.

EXPERT OPINION

Dr. Patel Jatin Jayeshbhai, MBBS, DVD, DNB, MNAMS

Pruritus is the most common problem in dermatological conditions. I noticed patients complain of sleep disturbances and reduced quality of life. It is associated with secondary skin lesions and change in DLQI scores. Hydroxyzine is used as first line therapy toward pruritus management at a bed time dosage. Its sedative effects make it a better drug in psychogenic pruritus. Patients treated with hydroxyzine reported improved DLQI scores. It is also used in management of severe pruritus due to dermatological cause, psychogenic pruritus, renal pruritus, and urticaria. It is safe and tolerable in patients.

Dr. K G Singh, MBBS, MD Skin and VD

Pruritus is a common symptom observed in patients. Dermatological conditions such as xerosis, eczema, psoriasis, non-dermatological causes, and side effect of certain medications are some of causes for pruritus. All these patients had reduced sleep with diminished quality of life. Prurigo nodularis is a complication associated with pruritus. Hydroxyzine is widely used as symptomatic treatment and trusted drug in chronic pruritus. It works better for patients suffering with night time pruritus. Patients treated with hydroxyzine had improved DLQI scores. It is considered as first line drug of choice in patients with chronic pruritus. It is devoid of drug-drug interaction and it reported to be safe and tolerable drug.

Dr. K. Karthikeyan, MBBS, MD (DVL)

Pruritus is a common symptom observed in 60% of patients. The common causes associated with pruritus are urticaria, psoriasis, and scabies. Patients are affected with sleep and quality of life. Eczema and secondary infections are the common complications reported in pruritus patients. Hydroxyzine that acts on both centrally and peripherally exhibits good therapeutic efficacy along with safety profile. It improves quality of life in patients. Sedative property of drug makes it unique when compared with other antihistamines. It is also preferred as drug of choice in other conditions like urticaria.

Dr. M. Sreenivasa Reddy, M.D

I had noticed pruritus as a common symptom in dermatology clinics. The common causes associated with pruritus in these patients are urticaria, eczema, and insect bites. Patients are presented to clinic with reduced sleep and quality of life. It is also associated with secondary complications and lichenifications. Hydroxyzine acts both centrally and peripherally and exhibits good therapeutic efficacy along with safety profile. It increases quality of life in patients. I choose to prefer hydroxyzine in other conditions such as urticaria, papular urticaria, and neurodermatitis.

Dr. Mahaveer Prasad Gupta, MBBS. DDV Skin and Venereal disease

In my routine clinical practice, I have experienced 60% of patients presented with a condition of pruritus. The common causes are atopic dermatitis, fungal conditions, and psoriasis. Sleep disturbances and reduced quality of life are common complaints reported in these patients. It is also

associated with scratch and secondary infections. I personally prefer hydroxyzine as a treatment choice. It exhibits good therapeutic efficacy along with safety profile. It increases quality of life in patients. It is also preferred drug of choice in other conditions such as pruritus and fungal conditions.

Dr. Pradip Kumar Sahana, MBBS. DVD. MD (DERM and VEN)

Pruritus is commonly reported in almost 90% of patients. The common causes associated with pruritus are xerosis, eczema, urticaria, psoriasis, and renal insufficiency etc. I noticed that these patients had a reduced sleep with diminished quality of life. Hydroxyzine acts both centrally and peripherally and exhibits good therapeutic efficacy along with safety profile. It improves quality of life in patients. It is also preferred drug of choice in other conditions in children with urticaria and pruritic dermatosis.

Dr. Prakash Khushiramani, MBBS, DDV

Pruritus is a common symptom reported in patients. Lichen simplex and atopic dermatitis are common causes associated with pruritus. Patients are affected with sleep disturbances, performance, and quality of life. Hydroxyzine acts both centrally and peripherally and exhibits good therapeutic efficacy along with safety profile (very few 1-2% patients had drowsiness). It enhances quality of life in patients and is very potent when compared with other antihistamines. It is also preferred drug of choice in other conditions such as atopic dermatitis and neurodermatitis.

Dr. Pramod Kumar Agarwal, MBBS.MD (Skin and VD)

Pruritus is a common symptom reported in eczema patients. Dermatological causes include fungal diseases, xerosis, and psoriasis. Non-dermatological causes include insect bites and side effects of certain medications. Sleep disturbances are common in these patients. Hydroxyzine is prescribed as treatment of choice in these patients due to its good therapeutic efficacy along with safety profile. No drug-drug interactions are reported in patients. It enhances quality of life in patients and is effective when compared with other antihistamines. It is used as first line treatment option in severe pruritus.

Dr. Ranganath Bharadwaj, MBBS. DVD

It is a quite common condition reported in clinics. The causes for pruritus include xerosis, eczema, psoriasis, diabetes, chronic kidney disease, and insect bites. Patients are affected with sleep disturbances and quality of life. It is associated with lichen simplex chronicus and Prurigo nodularis is complications. Hydroxyzine acts on both centrally and peripherally, with good efficacy along with safety profile in all age groups. About 90–100% enhanced quality of life is observed in hydroxyzine treated patients. I choose to prefer hydroxyzine as drug of choice in xerosis, eczema, burning sensation, chronic kidney disease (CKD), diabetes, itch, snake bite, and senile pruritus.

Dr. S. Sandip Arsad, MBBS. DVD

I noticed pruritus as a common problem in patients attending dermatology clinic. Dermatological causes include scabies, urticaria, and atopic dermatitis. Non-dermatological causes include renal and hepatic pruritus. Patients often had a disturbed sleep and decreased quality of life. Patients are presented with complications such as sleep disturbances, reduced quality of life, and secondary skin changes. Hydroxyzine is used in the treatment of pruritus due to its therapeutic efficacy and better safety profile. It reduces stress associated with pruritus and enhance quality of life in patients. Hydroxyzine is considered as drug of choice in other conditions such as urticaria, atopic dermatitis, and prurigo nodularis.

Dr. Suneel Vartak, MBBS, DVD

Pruritus is common dermatological disease in patients. The causes associated with pruritus are scabies, urticaria, fungal infections, renal, and hepatic diseases. This condition reduces patient sleep patterns and reduce quality of life. Patients with pruritus are associated with complications such as sleep disturbances, diminished quality of life, and secondary skin changes. Hydroxyzine works at both central and peripheral regions in brain and exhibits good efficacy along with safety profile. However, sedation was reported in patients prescribed with hydroxyzine hence administered during night. It enhances DLQI scores in patients and thus improves quality of life. It is preferred drug of choice in almost all pruritus condition.

Dr. Swati Gangan, MBBS, PGDCC, PGDMT

Pruritus is very common in my routine clinical practice. Dermatophyte infection, senile pruritus, and eczema are common causes for pruritus. Patients visit to clinic with disturbed sleep patterns and decreased quality of life. Hydroxyzine is a first generation H1 anti-histamine that works both centrally and peripherally. It reduces itch and increase DLQI scores. This drug is used widely in patients because of better efficacy and safety profile. It is considered as drug of choice in patients with dermatophytes infection.

Dr. Dharmendra Godara, MD Skin and VD

Nearly 5–6 patients in dermatology clinic are presented with symptom of pruritus. According to my opinion, dermatological causes include atopic dermatitis, taenia infections, psoriasis, and non-dermatological cause includes diabetes. Patients may often complain with disturbed sleep patterns and decreases quality of life. Secondary infections are observed in pruritus patients. Hydroxyzine is used in pruritus patients to manage the condition. It also exhibits good therapeutic efficacy along with safety profile. Patients treated with hydroxyzine therapy are benefited with reduced itch and enhanced quality of life in patients. It is preferred drug of choice in pruritus.

Dr. Abraham KA, MBBS, DVD

In my clinic, I had noticed many patients with a condition of pruritus both dermatologic and non-dermatologic causes are involved in these patients. Patients with pruritus suffered with reduced sleep, decreased quality of life associated with complications such as eczema, secondary infections, fever, and insomnia. I personally prefer to treat these patients with Hydroxyzine due to it is a good therapeutic efficacy and safety profile. In my clinical experience, patients treated with this drug had minimized itch scores and enhanced quality of life. Apart from pruritus, I choose to prefer hydroxyzine as drug of choice in other conditions such as pruritus and eczema.

Dr. Anil Bhokare, MBBS, DVD

Pruritus is very common condition reported in patients in my clinic. Dryness, infection, thyroid, senile, and renal conditions are causes associated with pruritus in these patients. It affects sleep and hampers quality of life. I choose to treat these patients with hydroxyzine to improve disease condition. In my experience, I noticed that hydroxyzine reduced itch and improved quality of life in these patients. It has mild sedative action and might be helpful in stress relief. I personally considerer hydroxyzine as drug of choice in pruritus with disturbed quality of life.

Dr. Anu Anna Varghes, M B.B S,D.V D.,F R.G.U H.S

Patients with pruritus are common in dermatology. Eczema, atopic dermatitis, and systemic disease such as diabetes are reported to be some of the causes for pruritus in these patients. I often observed that these patients had reduced sleep and decreased quality of life. Secondary infections and lichenification are complications associated with pruritus condition. I prefer to treat these patients with hydroxyzine. It acts both centrally and peripherally and exhibits good therapeutic efficacy along with tolerability. Patients respond faster with this drug. Patient's quality of life and itch scores were improved with hydroxyzine therapy. It is preferred drug of choice in conditions such as eczema and urticaria.

Dr. Rajesh Aggarwal, M.B.B.S. M.D

Pruritus is common symptom of dermatological disease. Some of the causes reported in patients with these condition are urticaria, scabies, fungal, and eczema. Many patients have reduced sleep and quality of life. Patients with these condition had anxiety as a complication. I prefer to treat such patients with hydroxyzine. They tolerated this drug well with improved quality of life. I choose to prefer hydroxyzine as drug of choice in the treatment of acute urticaria.

Dr. Rajina, MBBS,DDVL, DNB (Dermatology)

Pruritus being a primary symptom in a diverse range of skin diseases, 60–70% cases present to my clinic with pruritus. Dermatological eczema, urticaria, lichen planus, vesiculobullous disorders, collagen vascular diseases, infections like scabies, superficial fungal infections, and non-dermatological causes such as chronic renal failure, hepatic conditions such as cholestatic jaundice, endocrine conditions such as hypothyroidism, hematological conditions such as PCV are causes for pruritus. I noticed patients complain of reduced sleep and diminished quality of life. These patients end up with development of other complications such as secondary infections and lichenification of lesions. My personal choice of drug to treat these patients is Hydroxyzine. It should be used cautiously in elderly population. It increases total sleep time and reduces sleep awakening and latency, there by improve overall well-being of patients with chronic pruritic conditions. It is a preferred drug of choice in urticaria and atopic dermatitis.

Dr. Anand Kumar, MBBS, MD DVL

More than 20% of patients are observed with pruritus in my clinic. Senile pruritus, anemia, liver failure, and renal failure are some of the causes associated with pruritus. Patients of pruritus often complain with disturbed sleep pattern and hampered quality of life. Complications associated with pruritus include sleep deprivation, anxiety, and depression. I prefer hydroxyzine as a treatment option in these patients. It works both centrally and peripherally and exhibits good therapeutic efficacy along with safety profile. Patients treated with hydroxyzine therapy had improved quality of life and itch scores. I prefer hydroxyzine as drug of choice in conditions such as acute urticaria, scabies, and senile pruritus.

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Review Article

Recent Advancements in Materials Used in Implant Rehabilitation: A Review

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Abstract

Implant rehabilitation has been made from titanium, gold, alumina, zirconia, and glass materials. The long-term prognosis of an implant restoration depends on meticulous care taken in the diagnosis and the treatment planning for the patient. While titanium abutments are by far the most used and show excellent success rates, their grayish color and the possibility of corrosion and degradation render them less attractive. Before the introduction of zirconia, alumina abutments were used mainly in the anterior zone and for single-tooth replacement, and these were associated with high success rates. Yittria-stabilized zirconia abutments benefit from increased fracture toughness and flexural strength. Hybrid abutment crowns can also be made from lithium disilicate, zirconia-lithium silicate, and hybrid resin-matrix ceramics. High impact polymers have been introduced as dental abutments or framework materials to support single crowns to full-arch reconstructions. Poly-ether-ether-ketone (PEEK) is a sub family of the poly-aryl-ether-ketone. PEEK is a high performance thermoplastic linear homopolymer composed of similar repeating units.

Key words: Hybrid abutment crowns, Implant rehabilitation, Poly-aryl-ether-ketone, Poly-ether-ether-ketone, Yittria stabilized zirconia

INTRODUCTION

Dental implant therapy has dramatically expanded the treatment options available for both the partially and completely edentulous patient.[1] Implant supported overdentures and hybrid prosthesis often provide support for the soft tissues of the face when compared to the traditional fixed prosthesis, with the emergence of computer-aided designs and the development of prosthetic materials.[2] Implant rehabilitation materials have been made from titanium, gold, alumina, zirconia, and glass materials.[3] The long-term prognosis of an implant restoration depends on meticulous care taken in the diagnosis and the treatment planning for the patient.[1]

IDEAL REQUIREMENTS OF IMPLANT REHABILITATION MATERIALS

Requisites of an ideal implant restorative material[4]

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- It should be stable in the oral environment and should not undergo rapid corrosion.
- It should fit passively over the various implant abutment.
- It should be esthetic.
- It should not induce undue amount of stresses in the implant or the bone.
- It should be biocompatible and should not induce any allergic reaction.
- It should be easy to fabricate and handle.
- It should be cost-efficient.

RECENT ADVANCEMENTS IN IMPLANT REHAB MATERIAL

PEEK

Poly-ether-ether-ketone (PEEK) is a sub family of the poly-aryl-ether-ketone (PAEK). PEEK is a high performance thermoplastic linear homopolymer composed of similar repeating units. PEEK imparts its stiffness from aromatic benzene rings and its ability to rotate in an axial direction thanks to ether oxygen bonds.[5] PEEK implants rehabilitation materials can be produced using readily available 3D Printers.[6] Modified PEEK materials are also used to construct removable partial denture frameworks, resin-bonded FPDs, conventional bi-layered FPDs, and

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crowns and retentive clips on implant bars. PEEK materials are less prone to surface roughness when compared to composites.[7]

Poly-Ether-Ketone-Ketone (PEKK)

PEKK is a semi-crystalline thermoplastic in the poly-aryl-ether-ketone (PAEK) family, with high heat resistance, chemical resistance, and the ability to withstand high mechanical loads. PEKK's glass transition temperature (Tg) is 162°C. PEKK replaces one of the flexible Ether linkages with a more rigid Ketone group**.** This increases the glass transition temperature (Tg)– where the material first begins to soften– by about 15°C. PEKK is easier to 3D print than PEEK (i.e., better layer adhesion), all while offering similar strength and resistance properties (i.e., better dimensional accuracy). PEKK was introduced more recently and has an 80% higher compressive strength and better long-term fatigue properties than unreinforced PEEK. The prosthesis design with PEKK framework material may be contraindicated for patients with opposing fixed dental prostheses or natural dentition, a history of bruxism, or unfavorable implant distribution.[8]

DEI® Experience (Microhybid Composite)

It is a micro hybrid composite summing up the knowledge acquired in the years over this important category of composites and taking advantage of its potentialities. DEI® experience is produced using modern manufacturing technologies and has optimal formulation for achieving high resistance and elasticity (respectively, 350 and 130 Mpa) and exceptional esthetics and shine. These features allow its use either at dental practice or at laboratory for preparation of bridges and crowns. It has excellent and esthetic surface smoothing and good stability of the color with particle size from 0.02 micron to 1 micron and a total filler content of 80%.It has a high compressive strength of 350 Mpa and fluorescence.[9]

SR Nexco (Fibre-Reinforced Composite)

SR Nexco paste is a purely light-curing fibre reinforced laboratory composite with micro-opal fillers which allows to achieve a lifelike shade even if space is limited. SR Nexco Paste restorations achieve a durable shade stability and a lasting gloss as a result of the polymerization process. SR Nexco is particularly suitable for restorations supported by metal-based frameworks, framework-free implant supported restorations, and prosthetic gingiva reconstructions. The composition of SR Nexco features a high content of micro-opal fillers. As a result, the optical properties of the restorations are comparable to those of natural teeth: The opalescent and fluorescent characteristics are extremely lifelike. A harmonious shade match is achieved in different restorations and under varying light conditions. Application on zirconium oxide frameworks – SR Nexco also unfolds its well-balanced physical and processing properties on zirconium oxide frameworks. Due to the micro-opal fillers, the restorations are imparted with lifelike translucency, opalescence, and fluorescence. The frameworks are prepared and the materials applied in the same way as in the veneering of metal frameworks.[10]

Telio-Computer-Aided Design (CAD) (Modified Cross-Linked PMMA)

Telio® CAD is CAD/computer-aided manufacturing (CAM)-fabricated implant-supported hybrid abutment crowns for individual and temporary single-tooth reconstructions. The material consists of a cross-linked polymer block (PMMA), enabling the fabrication of individual, monolithic hybrid abutment crowns which are directly cemented to a titanium bonding base. Shape, esthetics, and emergence profile can be easily designed and adjusted any time. The monolithically milled hybrid abutment crown is extraorally cemented to the titanium bonding base by means of multilink hybrid abutment. Then, the restoration is screwed onto the implant. The screw channel is sealed with a composite or a light-curing temporary restorative material. As a result of the industrial polymerization process, the blocks feature a high material homogeneity. Polymerization shrinkage or inhibition layers no longer have to be taken into consideration. Stains and/or layering materials can be used to apply final esthetic optimizations. It has a flexural strength up to 135 Mpa and solubility ranging from 7.5 to 0.0018 $\mu g/mm^3$.[11]

SR Adoro (Nanocomposites)

The advantageous properties of SR Adoro can be attributed to the high proportion of inorganic fillers in the nanoscale range. Furthermore, the matrix is based on a urethane dimethacrylate (UDMA), which has also been newly developed and which is characterized by its toughness, which is higher than that of its predecessors or the frequently used Bis-GMA. The material demonstrates color stability as well as outstanding enamel-like luster and natural opalescence. The range of indications of the SR Adoro veneering composite includes removable denture prosthetics (e.g., telescope crowns and model cast dentures) and fixed dental reconstructions (veneering material for metal or fiber reinforced frameworks).[12]

IPS e.max (Lithium Disilicate)

Lithium disilicate (LS_2) glass-ceramic is ideally suitable for the fabrication of monolithic restorations or veneered restorations in the anterior and posterior region. Due to its natural-looking tooth coloring and excellent light-optical properties, this material produces impressive results. experience. The material is used in the dental laboratory in conjunction with either press or CAD/CAM technology.

Years of clinical experience confirm the high strength of 500 MPa* for IPS e.max lithium disilicate. The outstanding performance of the material is based on a combination of excellent flexural strength and high fracture toughness adjusted to the given dental requirements.[13]

IPS e.max Press

Customized results: Implant-supported hybrid restorations using the press technique.

IPS E. max Press is used to create individual, aesthetic hybrid abutment restorations in combination with Viteo base titanium bonding bases. Two options are available for this purpose:

- Hybrid abutments

The hybrid abutment is an individually pressed lithium disilicate abutment, which is bonded to a titanium bonding base, for example, Viteo Base.

- Hybrid abutment crowns.

A hybrid abutment crown combines the abutment and crown in one. It is monolithically pressed and then securely bonded to the titanium bonding base with the help of Multilink Hybrid Abutment and subsequently screwed in place.[13]

IPS e.max CAD

IPS e.max CAD abutment solutions are designed for the fabrication of implant-supported hybrid structures for single teeth using CAD/CAM technology. The hybrid components are individually milled from lithium disilicate blocks (LS_2) and bonded to a titanium bonding base. This temporary restoration offers many options in terms of soft-tissue management and forms the basis for an aesthetic and functional permanent IPS e.max CAD restoration. The strong bond between the lithium disilicate glass-ceramic (LS_2) and the titanium bonding base is established with the specially formulated luting composite multilink hybrid abutment.[13]

3M Lava Esthetic (5% Yttrium Stabilized Zirconium Oxide)

3M™ Lava™ esthetic fluorescent full-contour zirconia discs are pre-sintered mill blanks used for the fabrication of esthetic, full-contour zirconia restorations. The restorations are designed using dental CAD software, and the data are converted into milling paths by CAM software. Subsequently, the discs are processed in milling units suitable for pre-sintered zirconia. Milled restorations must be finally sintered in a furnace suitable for zirconia, using the cycle designated for Lava esthetic zirconia. The discs are available in various heights and shades based on the VITA classical A1-D4® shade guide. All discs are pre-shaded with a shade gradient set vertically in the blank that becomes visible after sintering. With a flexural strength of 800 MPa and a high translucency, Lava esthetic zirconia is ideal for esthetic full-contour restorations including 3-unit posterior bridges. The material formulation is a composition of "zirconia" (zirconium dioxide, ZrO2) with a small addition of "yttria" (diyttrium trioxide, Y_2O_3). Final sintering at 1500°C for 2 h produces a dense polycrystalline microstructure. The shading elements are distributed and built into the crystals to provide the desired shade gradient and tooth-like fluorescence.[14]

3M LAVA Plus (3% Yttrium Stabilized Zirconium Oxide)

3M™ Lava plus zirconia discs are pre-sintered mill blanks used for the fabrication of esthetic and full-contour zirconia restorations. The material formulation is a composition of "zirconia" (zirconium dioxide, ZrO2) with a small addition of 3% "yttria" (diyttrium trioxide, Y2O3). The yttria content determines the so-called "phase" of the crystals, that is, how the Zr and O atoms are arranged. It has a flexural strength of 1100 Mpa and afracture toughness of 5–10 Mpa.[15]

CERCON® ALL CERAMIC (YTTRIUM – TETRA POLYGONAL ZIRCONIA (TZP) STABILIZED ZIRCONIA)

Cercon ht blanks are made of yttrium oxide- (yttria-) stabilized zirconium oxide (zirconia) (Y-TZP). They are used in fabricating frameworks for fixed prosthetic restorations. In contrast to conventional dental ceramics, Y-TZP is composed of many small particles without any glassy phase at the crystallite border.[16]

Cercon® HT (5% Yttrium TZP Stabilized Zirconia)

Depending on the framework design, cercon ht frameworks can be ceramically veneered or delivered as fully contoured restorations.

Cercon® XT (9% Yttrium TZP Stabilized Zirconia)

Cercon® XT demonstrates extra high translucency and unparalleled shade accuracy with life-like esthetics especially for the anterior region (flexural strength: 750 MPa).

NANOZR (CERIUM – TETRA POLYGONAL ZIRCONIA (TZP) STABILIZED ZIRCONIA)

Ceria-stabilized tetragonal zirconia-based nanocomposite ceramic (nano-zirconia) was a material which was developed by Nawa *et al.* This material inculcates nanosized alumina particles into the crystal grains of tetragonal zirconia (Ce-TZP), which are then stabilized with ceria. NANOZR is usually composed of 10 mol% of CeO_2

stabilized TZP as a matrix and 30 vol% of Al_2O_3 as second phase. The average size of the NANOZR is 0.49 μm. The significant characteristic of its structure is its intragranular-type nanostructure in which several 10–100 nm sized Al_2O_3 particles are trapped within the ZrO_2 grains. The raw material powder of NANOZR mainly consists of zirconium oxide (ZrO2), cerium oxide (CeO_2) as a stabilizer, and also alumina (Al_2O_3). Since alumina is present at 10 wt% or more, there is no translucency, and the color tone is pale yellow due to the effect of cerium oxide. The crystal structure is the eutectic of tetragonal zirconia and alumina. In addition, toughening is achieved by the formation of a nanocomposite structure in which the respective nanoparticles mutually diffuse in zirconia and alumina particles.[17]

VITA IN CERAM YZ CUBES FOR CEREC (ZIRCONIUM OXIDE)

Zirconium oxide is an oxide ceramic material with superior flexural strength among oxide ceramic materials. This results from the possibility of stabilizing ZrO_2 in its denser high temperature phase through the appropriate addition of yttrium oxide. Zirconium oxide is also referred to as "ceramic steel". This property also ensures the high durability of zirconium oxide under permanent load. VITA In-Ceram® YZ Cubes for CEREC® are presintered zirconium oxide blocks partially stabilized with yttrium oxide. In this condition that allows easy processing, they are used to grind enlarged bridge and crown substructures in the CEREC inLab system. Then, these structures are sintered (dense sintering process) in a special high temperature furnace so that they shrink and form highly stable and precision-fit structure which offer all physical benefits of zirconium oxide. The material can only be processed in Cerec 3/inLab, software update version 1.40 R950 (or higher) of Sirona Co.[18]

CONCLUSION

With newer materials being introduced in implant dentistry, it is imperative to acquire knowledge about various materials available and understand the factors, which will contribute to the success or failure of the restorations.[6] A polychromatic feldspathic CAD/CAM ceramic material can yield optical esthetics and a novel CAD/CAM hybrid ceramic material can provide sufficient fracture strength and load capacity for the posterior area. It maintains esthetics and masticatory functions and restores healthy periodontal and peri-implant conditions. Implant dentistry and dentistry in general will witness more applications of PEEK materials in the near future, mainly because of PEEK's ability to be modified using a wide range of materials and techniques. The concept of combining a costabilized zirconia with a dispersion of alumina and/or hexa aluminates provides a variable basis to design composite ceramics with a broad range of properties. Partial substitution of the alumina dispersion by strontium hexa aluminate can improve the strength and preserve toughness, hardness, and low-temperature degradation resistance.[8]

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Review Article

Ghrelin and Its Role in Therapeutics

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Abstract

Ghrelin, derived from the word "ghre" referring "to grow," is a multifaceted hormone containing 28 amino acids produced from X/A cells of oxyntic glands in stomach. Pituitary gland regulates growth of various organs through hormones which, in turn, are controlled by a master switchboard, the hypothalamus. Ghrelin functions by increasing the release of growth hormone (GH) and plays a key role in endocrine system. The name ghrelin may wrongly make us think that it acts through GHRH, but it has receptor named GH secretagogue-receptor having a wide distribution and its therapeutic actions are not limited to one system. Its localization with dopamine receptor in hippocampus, hypothalamus, and striatum makes ghrelin to exert neuroprotective effect. Main physiological role of ghrelin is to regulate food intake and has orexigenic properties. Ghrelin has a short half-life due to degradation by proteases, and thus, ghrelin mimetics are employed as therapeutic agents. Ghrelin is regulated by acylation with the acylated form being active. Drugs affecting ghrelin functions are being evaluated for various conditions including cancer cachexia, diabetic gastroparesis, post-operative ileus, and fibromyalgia. This review will deal about the physiological functions of ghrelin, its possible therapeutic indications, approved drugs, and drugs in trials.

Key words: Ghrelin mimetics, Ghrelin, Growth hormone

INTRODUCTION

In the year 1976, Bowers *et al.* found that opioid peptide had no opioid activity but had mild growth hormone (GH) releasing property and they referred it as GH secretagogues which was found to act through receptor GH secretagogue receptor 1a (GHS-R1a), while GHS-R1b, the truncated form of the receptor, is found to be without any clear action. In 1999, endogenous ligand was identified from rat stomach and it was known as ghrelin taking its base from a word "ghre" meaning "to grow."[1] Ghrelin is a peptide which causes orexia by acting as regulator of food intake and since it stimulates release of GH, its use is also utilized in GH deficiency.

STRUCTURE

Human ghrelin gene is present in chromosome 3p25–26. After it undergoes transcription and translation, it yields preproghrelin precursor containing 117 Aminoacids (AA) and the final peptides formed include ghrelin with 28 AA and obestatin having 23 AA. Ghrelin is a peptide which is 28 in number and exerts its action by binding to GHS-R1a which is a seven transmembrane GPCR. It exists in 2 forms as acylated and desacylated. Acylated form is essential for ghrelin action (Figure 1). Ghrelin-O-acyl transferase is essential for the acylated form which is an unique post-transcriptional modification at 3rd position and plasma proteases have a role to degrade circulating ghrelin. Suppression of acyl ghrelin is related with acute exercise whereas increased des-acyl ghrelin results due to weight loss.[2] Recent evidence showed that desacylated ghrelin can also function as an independent hormone and can act as endogenous antagonist for acylated ghrelin at supra-physiological concentration.[3]

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LOCATION

Ghrelin receptors are ubiquitously present both centrally and peripherally with its central distribution maximum in hypothalamus and peripheral tissues distribution maximum in stomach and also seen in heart, pancreas, kidney, and vasculature. Ghrelin is produced in maximal amount from X/A like cells which are present in fundus of stomach.

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REGULATION OF GHRELIN SECRETION

Ghrelin secretion is regulated by the following factors. The positive regulators include fasting, parasympathetic nervous activity whereas negatively regulated by food intake, sympathetic nervous activity, and leptin.

Physiological Functions and its Possible Indications

Central nervous system

Regulation of food intake

Ghrelin has a very important role in regulation and control of food intake. It is considered to be a signal for hunger. When hunger develops in the presence of decreased nutrients to brain, ghrelin levels gets raised and this plays as an orexigenic peptide to stimulate feeding center present in hypothalamus. After food intake, levels of ghrelin fall down and this causes a feeling of fullness. Ghrelin has opposite action of leptin and this activates NPY/AgRP neurons to stimulate food intake is shown in Figure 2.[4] The molecular mechanisms involved in regulation of food intake is shown in Figure 3. [5]

Higher brain functions

Ghrelin is found to increase dopamine release from ventral tegmental area and this has a role in reward system. Colocalization of ghrelin receptors with dopamine receptors and dimerization of them in hippocampus, striatum, and arcuate nucleus helps in learning, memory, and improves synaptical plasticity.[6]

Taste

Two systems are present in taste cells which have role in transduction of taste. They include Amiloride-sensitive and insensitive and this is differentiated based on their response to Amiloride (ENaC blocker). There is coexpression of ENaC with ghrelin and this has been found in animal studies. Ghrelin is found to have role in transmitting taste sensation to CNS by increasing serotonin levels in nucleus accumbens.[7]

Indication

Ghrelin agonists MK-0677 and LY444711 have found to have protective role in Alzheimer's disease (Figure 4) in animal studies by following mechanisms.[8]

Endocrine role

GH releasing function

Ghrelin being a GH release facilitator finds its use to find out, whether there is GH deficiency or not.

Indication

Macimorelin acts by increasing GH release and this is used to find out deficiency of GH after the drug is given orally.[9]

Relation with cortisol

Cortisol is considered to be involved in stress and it increases level of ghrelin to increase food intake.[10]

Reproduction

Ghrelin decreases LH and FSH levels and delays the development of puberty. Dysregulation of ghrelin secretion has been observed in Polycystic Ovarian Syndrome.[11]

Glucose homeostasis

Ghrelin and insulin are inversely related and increase in ghrelin levels leads to hyperglycemia. Ghrelin exerts this action by stimulating secretion of glucagon and inhibiting insulin secretion (Figure 5). *Ghrelin has only role in low-energy balance to maintain glucose homeostasis*.[12]

Indication

On long-term treatment with ghrelin receptor antagonist [D-Lys3]-GHRP-6 in animal studies, it worsened the diabetes most likely due to desensitization of the receptor on long term.[13] Hence, the use of ghrelin receptor antagonists for diabetes mellitus requires further research.

Heart

Ghrelin is found to have cardioprotective effect (Table 1) by the following mechanisms.[14]

- Stimulation of Akt/Mitogen-activated protein kinase pathway which is highly proliferative and exerts anti-apoptotic effects. This property is utilized in cardiac cachexia.
- Inhibits sympathetic system causing vasodilation.
- In preclinical studies, it is found to increase growth by IGF-1-mediated actions leading to hypertrophy of heart.[15]

Adipose tissue

White adipose tissue functions to store fat, whereas brown adipose tissue will release heat which will help in thermogenesis. Ghrelin promotes fat storage by activating white adipose tissue, whereas and deactivates brown adipose tissue function by inhibits sympathetic system by deactivating brown tissue function. Thus, ghrelin acts like an orexigenic peptide causing weight gain.

Indication

- An endogenous ghrelin antagonist Liver-expressed Antimicrobial peptide 2 acts as negative regulator for ghrelin and it is found to reduce food intake and GH secretion in preclinical studies, thereby becoming a potential target for regulation of energy homeostasis.[6]
- Prader–Willi syndrome: It is a congenital obesity syndrome characterized by hyperphagia, GH deficiency, and dysmorphic features. In adults, due to obesity, ghrelin levels will fall due to the progression of the disease and loss of function of ghrelin.[16]

Liver

Ghrelin exerts fat storage in liver by inhibiting expression of AMP-activated protein kinase (AMPK) leading to

lipogenesis. This activates downstream pathways mTOR and PPAR-gamma which leads to hepatic steatosis (Figure 6). The anti-inflammatory action of ghrelin in liver prevents progression of non-alcoholic fatty liver disease to non-alcoholic steatohepatitis.[17]

Intestine

Ghrelin stimulates the gastric motility mediated by parasympathetic system.[18]

Indication

This property helps ghrelin to be employed in conditions such as diabetic gastroparesis and post-operative ileus, where the motility is decreased and ghrelin mimetics are in clinical trials for those conditions.

Bone formation

GHS-R1a is also seen in osteoblasts and ghrelin by activating this is found to increase bone mineral density (BMD) in animal studies.[19]

Indication

Serum ghrelin concentration predicts BMD and this is done in patients with anorexia nervosa.

Anti-inflammatory effect

Ghrelin downregulates GHS-R present in T lymphocytes thereby inhibits pro-inflammatory mediators release. The mediators include tumor necrosis factor-alpha, IL-6, and IL-1beta. Ghrelin also enhances the expression of IL-10 which is an anti-inflammatory cytokine and it also promotes thymopoiesis.

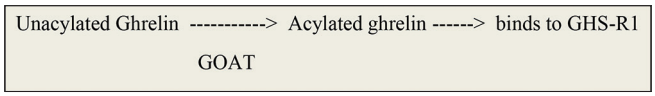

Figure 1: *Illustration of ghrelin metabolism in target tissues*: Unacylated ghrelin metabolized by Ghrelin-O acyl transferase (GOAT) forming acylated ghrelin which binds to Growth Hormone Secretagogue –Receptor 1 (GHS-R1) and exerts its actions.

Indication

- In animal studies, ghrelin has a protective role in sepsis by proliferation of CD4 T-cells. Ghrelin also exerts its action by inhibition of pro-inflammatory mediators and inhibition of High Mobility Group Box 1 protein.[20]
- Ghrelin agonist GH releasing peptide (GHRP-2) was found to decrease inflammation by inhibiting IL-6 in arthritic rats.[21]
- Parkinson's disease is characterized by degeneration of neurons and activation of microglia leading to release of inflammatory mediators. Ghrelin exerts neuroprotective effect by its anti-inflammatory property of decreasing IL-6 in animal model of Parkinson's disease.[22]
- *Whole body radiation and sepsis* induced in animals activates the sympathetic system and release norepinephrine. This stimulates Kupffer cells in liver to release inflammatory mediators which are inhibited by giving ghrelin through anti-inflammatory effect.[23]
- It inhibits nuclear factor-kappa B in endothelial cells and exerts its protective effect in atherosclerosis by decreasing inflammation.[24]

Table 1: Ghrelin as cardioprotective agent

Indications	Rationale for use
Coronary artery disease	Anti-inflammatory effect and regulate atherosclerosis
Hypertension	Vasodilation and decrease in sympathetic nervous activity
Cardiomyopathy	Inhibit myocardial apoptosis
Heart failure	Promote growth of heart and in cardiac cachexia (end-stage HF), used by acting as regulator of food intake and by its anti-oxidative effects.

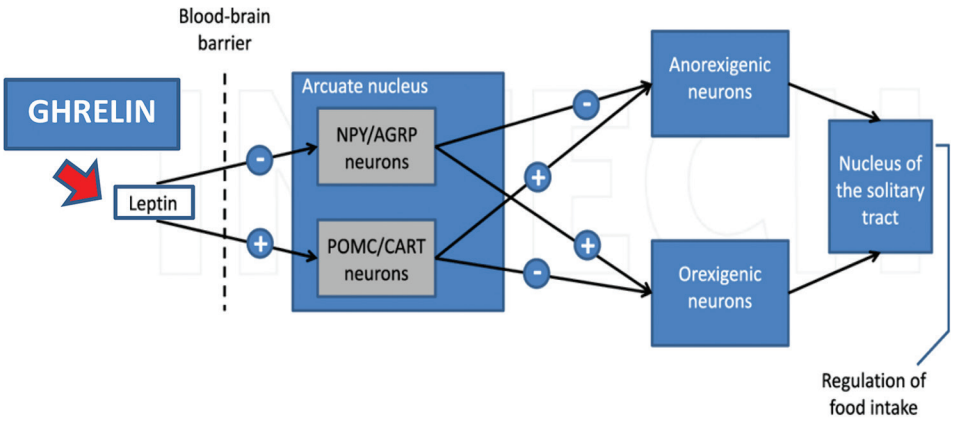

Figure 2: *Relation between leptin and ghrelin*. Ghrelin inhibits the activity of leptin and stimulates NPY/AgRP neurons to regulate food intake, leading to weight gain. NPY: Neuropeptide Y, AGRP: Agouti-related peptide, POMC: Pro-opiomelanocortin, and CART: Cocaine and amphetamine regulated peptide.[4]

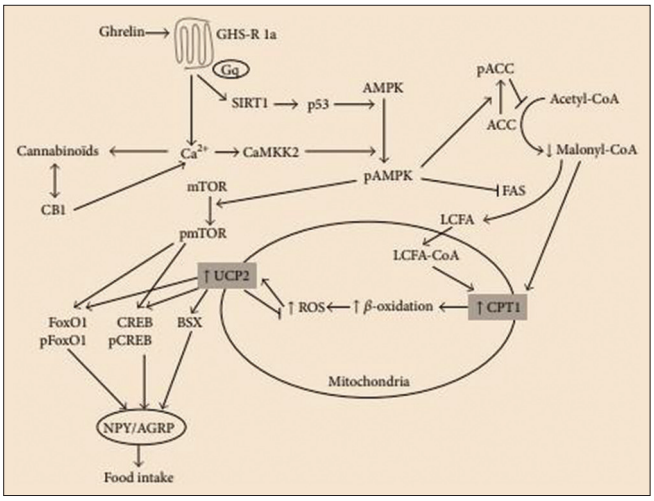

Figure 3: Molecular mechanisms involved in regulation of food intake. Ghrelin triggers a central SIRT1/p53 pathway and this leads to phosphorylation of AMP activated protein kinase (AMPK) leading to increased beta-oxidation and reactive oxygen species (ROS) production which stimulate UCP-2 to regulate food intake by stimulating NPY/AgRP neurons in arcuate nucleus of hypothalamus. SIRT1-sirtuin 1, AMPK-5' adenosine monophosphate activated protein kinase, CaMKK2-calmodulin kinase-kinase 2, CB1-cannabinoid receptor 1, ACC-Acetyl CoA carboxylase, FAS-fatty acid synthase, UCP2-Uncoupling Protein 2, CREB- cAMP response element binding protein, CPT1-carnitine palmitoyl transferase, BSX- Brain specific homeobox transcription factor, and FoxO1-factor forkhead box O.5

Muscle

It is found that ghrelin increases muscle growth by activation of insulin-like growth factor 1 in animal studies.

Indication

By this mechanism, it is used in cancer cachexia, where there are decreased muscle mass and impaired function of muscle thereby preventing muscle atrophy.[25]

Kidney

Degradation of ghrelin occurs through kidney and any dysfunction in kidney contributes for the increased plasma ghrelin concentration. Inflammation, energy homeostasis, and CVS factors play a key role in pathogenesis of chronic kidney disease.

Indication

Since ghrelin has protective role in all three pathways, it can be considered as a biomarker in end-stage kidney disease.[26]

Vasculature

The vasodilating property of ghrelin (Figure 7) is found in animal studies.[27]

Gastrointestinal Stromal tumor (GIST)

Ghrelin has a proliferative activity and this increases risk of GIST by PI3K/AKT/mTOR pathway which controls cell growth, proliferation, and differentiation.[28]

Table 2: Macimorelin[29]

Mechanism of action	Pharmacokinetic property	Dose	Interpretation	Precautions
Stimulates release of growth hormone by acting as a GHS-R agonist	Absorbed between 0.5 and 1.5 h. Metabolized by CYP3A4 Excreted in urine with half-life of 4 h.	Given as an oral solution at dose of 0.5 mg/kg body weight.	Serum GH levels of less than 2.8 ng/ml at time points 30, 45, 60, 90 min is considered GH deficient	Avoid giving drugs metabolized by CYP3A4, drugs increasing GH secretion. Oral solution to be given in *fasting of 8 h.*

Table 3: Drugs in pipeline

Drugs	Clinical indication	Phase of clinical trial*	Rationale of use
Anamorelin[31]	Non-small cell lung cancer-Cachexia (NSCLC-C)	Phase 3	To regulate appetite and increase lean body mass
	Osteopenia and Sarcopenia	Phase 1	To improve muscle mass and bone growth
Relamorelin[32]	Diabetic gastroparesis	Phase 3	To stimulate motility
	Anorexia nervosa	Phase 2	To improve appetite
	Chronic constipation	Phase 2	To stimulate motility
Ulimorelin[33]	Enteral Feeding Intolerance	Phase 2	To regulate appetite
	Post-operative ileus	Phase 3	To stimulate motility
Ipamorelin	Gastrointestinal dysmotility	Phase 2	Reduce time to recovery of GI function after partial small or large bowel resection
Ibutamoren (MK-0677)	Fibromyalgia	Phase 2	To stimulate growth hormone as patients with fibromyalgia are GH deficient.

*as reported in the http://www.clinicaltrials.gov

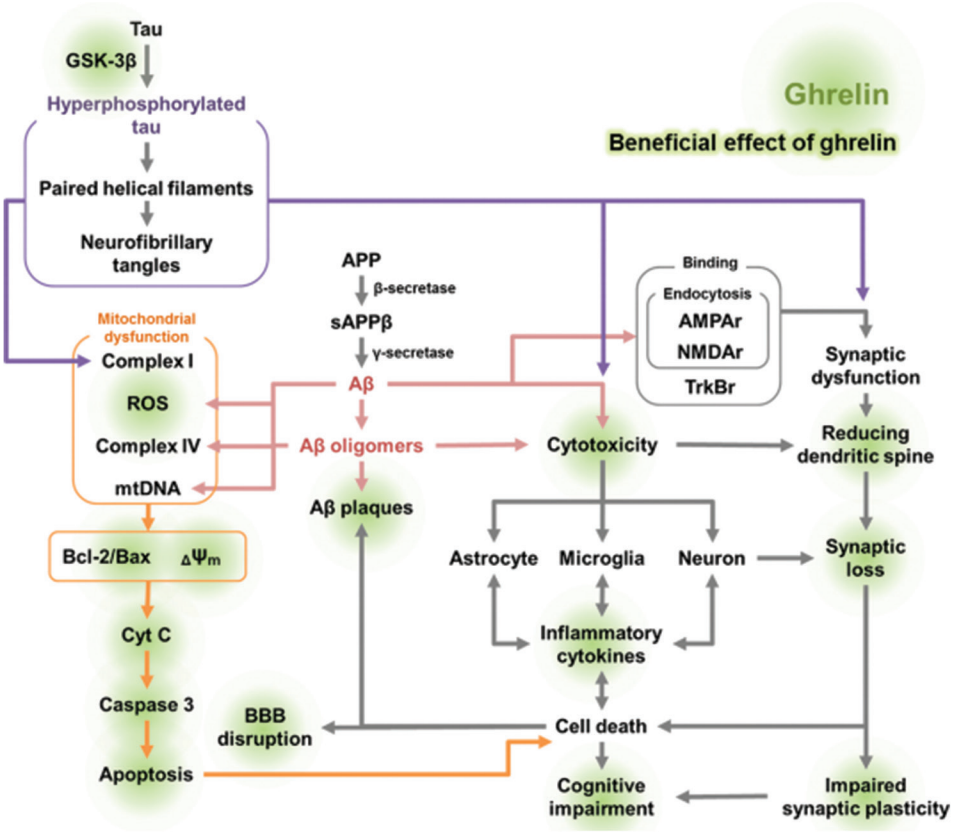

Figure 4: ***Therapeutic Use of ghrelin in Alzheimer's disease.*** **Ghrelin inhibits tau hyperphosphorylation by inactivating glycogen synthase kinase-3 β (GSK-3β) and reduces Aβ. It also reduces ROS by its anti-apoptotic effect and improves synaptic plasticity and cognition. APP-amyloid precursor protein, NMDAr-N-methyl D-aspartate receptor, TrkBr-Tropomysin receptor kinase B, and AMPAr-Alpha amino-3 hydroxy-5methyl-4isoxazolepropionic acid receptor[8]**

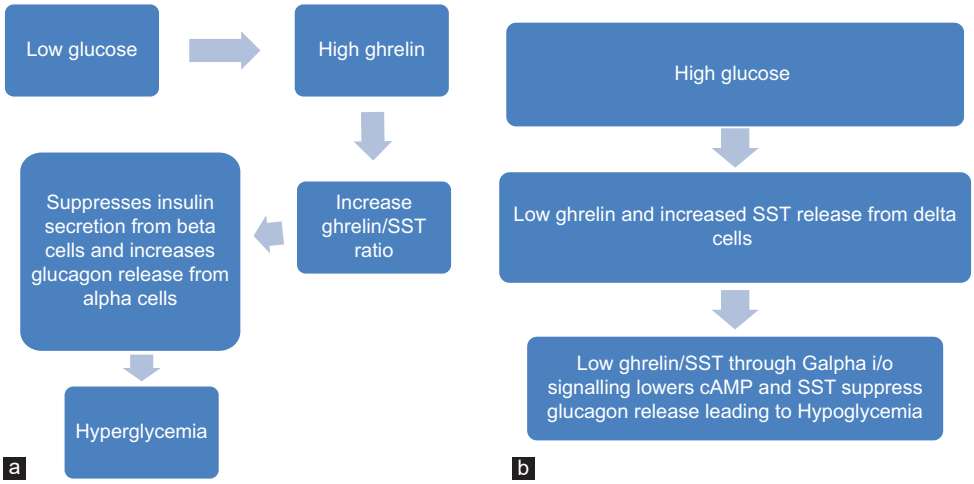

Figure 5: (a) In the setting of low glucose and (b) in the setting of high glucose[12]

APPROVED DRUGS

- Macimorelin is a non-peptide (Table 2) and got approved in the year 2017 by FDA.[29]
- The use of the drug is to find out whether the deficiency of GH is present or not. The test done is a provocation test.
- To measure GH levels, blood sample is drawn to determine levels at time points 30, 45, 60, and 90 min after giving the oral solution.
- Final concentration of the solution is made to 0.5 mg/ml after reconstitution of macimorelin granules in water.

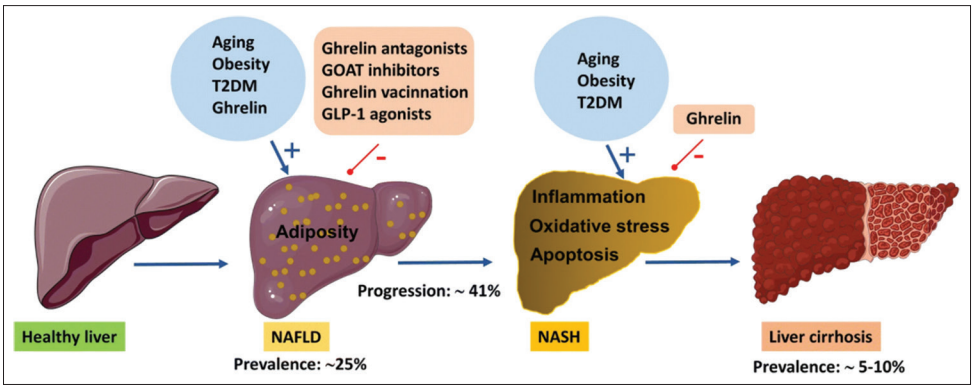

Figure 6: *Ghrelin have a dual action on liver*. Metabolic factors such as aging, obesity, and Type 2 DM are risk factors for NAFLD and NASH. Ghrelin promotes hepatic steatosis and by its anti-inflammatory and anti-apoptotic effect, which prevents the progression of NAFLD to NASH. NAFLD-Non-alcoholic fatty liver disease, NASH-Non-alcoholic steatohepatitis. GOAT-Ghrelin-O acyl transferase[17]

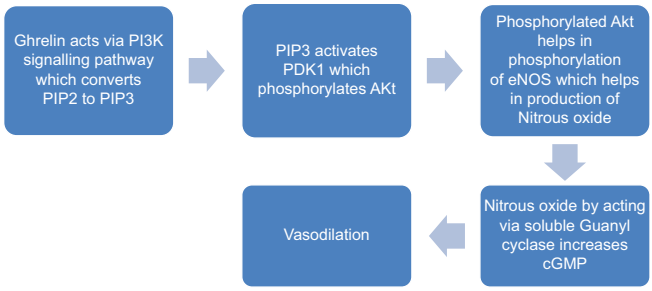

Figure 7: Vasodilator mechanisms of ghrelin

- The cutoff level of GH as 2.8 ng/ml is made from the phase 3 trials, where macimorelin is compared with insulin.
- Drugs affecting GH secretion should be avoided before doing the test as it may give false positive results.
- Drugs in pipeline for various conditions are shown in Table 3.

CAPROMORELIN

- It is a selective ghrelin receptor agonist approved by FDA in *dogs* in 2016.
- It is given orally at a dose of 3 mg/kg OD to stimulate appetite.[30]

CONCLUSION

Ghrelin has many protective effects as its release will be increased in different conditions such as restriction of calories, psychological stress and cachexia. Ghrelin mimetics show promising results in conditions involving gastrointestinal motility such as diabetic gastroparesis, post-operative ileus, and chronic constipation. It also shows promise in conditions to regulate food intake in cancer cachexia and anorexia nervosa, and hence, it is rightly called as a "Survival Hormone."

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Original Article

Major Amputations of Limbs in Vascular Surgical Unit of Cenhosoa Antananarivo

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Abstract

Background: Major amputations of limb are a major surgical procedure, associated with profound economic, social, and psychological effects on the patient and family. The aim of this study was to describe etiology and outcomes of major limb amputations in Vascular Surgical Unit of Cenhosoa Antananarivo.

Materials and Methods: This was a retrospective and descriptive study for a period of 10 years from January 2011 to December 2020, performed at Vascular Surgical Unit of Cenhosoa Antananarivo, including all patients underwent major amputation of limbs. Demographic data, surgical indications, cardiovascular risk factors, level of amputation, surgical procedures, and outcomes were analyzed.

Results: Eighty-seven patients were recorded, including 72 males (82.75%) and 15 women (17.24%). The average age was 56.34 years old. The reason of amputations was diabetic gangrene (62.06%), peripheral arterial disease (20.68%), embolism (9.19%), trauma (5.74%), and tumors (2.29%). The most risk factors of cardiovascular disease were male older (72.34%), high blood pressure (81.60%), diabetes mellitus (62.06%), and smoking (52.87%). Amputations were located in the lower limb for 85 patients (97.70%) and in the upper limb for 2 patients (2.29%). The most common levels of amputation were the thigh (55.17%) following by the leg (42.52%). Amputations were performed using regional anesthesia (72.34%) and general anesthesia (17.56%). The hospital mortality rate was 6.89%.

Conclusion: Diabetic gangrene was the most indication of major amputation of limb. Early detection and management of diabetes mellitus and other cardiovascular risk factors could reduce amputation rate in our patients.

Keywords: Amputation, Diabetes mellitus, Gangrene, Limb, Peripheral arterial disease

INTRODUCTION

Major amputation is common surgical procedures in vascular surgery, defined as the loss in the transverse anatomical plane at or above to the ankle or wrist joint. Amputation constitutes the latest therapeutical alternative in vascular or orthopedic surgery, used if the limb's salvage attitudes have been exhausted. The lower extremity amputation represents a significant burden on global health systems. There are nearly 2 million people living with limb loss in the United States and the main causes are vascular disease (54%), trauma (45%), and cancer (<2%).[1] In Europe, the average annual incidences of major lower limb amputations are approximating 30/100,000 population in the Central and Eastern European countries and 20/100,000 population in Western European countries.[2] The truth prevalence of major lower limb amputation in African countries remain unknown. However, few studies have been reported the prevalence of hospital of major limb amputation in sub-Saharan African literature. The aim of this study was to describe etiology and outcomes of major limb amputations in Vascular Surgical Unit of Cenhosoa Antananarivo.

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MATERIALS AND METHODS

Study Design

We conducted a retrospective and descriptive study for a period of 10 years from January 2011 to December 2020,

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including all patients underwent major amputation of limbs.

Study Setting

This was study conducted in Vascular Surgical Unit of Soavinandriana Hospital Center (Cenhosoa) Antananarivo. Soavinandriana Hospital Center is one of teaching hospital in Antananarivo, belongs to the Ministry of National Defence, and receiving all civilian or military patients. Vascular Surgical Unit in Cenhosoa is one of the reference vascular surgery units in Antananarivo, receiving all patients requiring vascular surgery.

Inclusion Criteria

All patients underwent major limb amputations and performed in Vascular Surgical Unit of Soavinandrina Hospital Center were included in this study.

Data Collection and Analysis

Data were collected from patients folders stored in Vascular Surgical Unit of Cenhosoa. We established questionnaires before collecting data, including all parameters: Demographic data, surgical indications, cardiovascular risk factors, location, and level of amputation and outcomes. Data collected were analyzed using SPSS® 21 statistics software program.

RESULTS

A total of 87 patients were recorded in this 10-year-period. The average age was 56.34 years old (from 26 to 71 years old). Population study was 72 males (82.75%) and 14 women (17.24%), giving a sex ratio of 4.80. The reason of amputations was diabetic gangrene (62.06%), peripheral arterial disease (20.68%), embolism (9.19%), trauma (5.74%), and malignant tumors (2.29%). Maligant tumors were osteosarcoma. The most risk factors of cardiovascular disease were male older (72.34%), high blood pressure (81.60%), diabetes mellitus (62.06%), and smoking (52.87%) [Table 1]. Amputations were located in the lower limb for 85 patients (97.70%) and in the upper limb for 2 patients (2.29%). The most common levels of amputation were above-knee (55.17%) and below-knee (42.52%) [Table 2]. Amputations were performed using regional anesthesia (72.34%) and general anesthesia (17.56%). Thirty-four patients (39.08%) have been presented local complications that the most common complications were surgical wound infection (12 cases) and wound hematoma (10 cases) [Table 3]. The hospital mortality rate was 6.89%. Causes for those deaths were three septicemia, two acute renal failure, and one pulmonary embolism.

Table 1: Surgical indications of amputation and cardiovascular risk factors

Indications		
Peripheral arterial disease	18	20.68
Diabetic gangrene	54	62.06
Embolism	08	09.19
Trauma	05	05.74
Malignancies	02	02.29
Cardiovascular risk factors		
Male>50 years/Female>60 years	68	78.16
High blood pressure	71	81.60
Diabetes mellitus	54	62.06
Smoking	46	52.87
Dyslipidemia	39	44.82
Sedentarity	9	10.34
Obesity	6	6.89

DISCUSSION

Major limb amputation is a common surgical procedure performed by orthopedic, general, vascular, and trauma surgeons for a vast number of therapeutic reasons. Amputation could influence of psychological, economic, and social of the patients as well as their families. In 2015, there were approximately 150,000 non-traumatic lower-extremity amputations in the United States.[3] Major amputation ranges from 5.6 to 600/100,000 in the population with diabetes and from 3.6 to 68.4/100,000 in the total population.[4] The incidence of major amputation varies by country. In Europe, the average annual incidences of major lower limb amputations are approximating between 20 and 30/100,000 population.[2] The truth prevalence of major amputation of limbs in sub-Saharan African countries remains unknown because all studies published the prevalence at a single teaching hospital. The prevalence of major amputation in sub-Saharan hospital was 172 cases for 2 years period in Cameroonian study by Alegbeleye,[5] 155 cases for 2 years period in Chadian study

Table 2: Location and level of amputation

Upper limbs (*n*=2)		
Above elbow	1	1.14
Below elbow	1	1.14
Lower limbs (*n*=85)		
Above knee	48	55.17
Below knee	37	42.52

Table 3: Outcomes and postoperative complications

Results		
Simple postoperative	47	54.02
Local complications	34	39.08
Death	6	6.89
Local Complications (*n*=34)		
Surgical wound infection	12	13.79
Wound dehiscence	5	5.74
Wound hematoma	10	11.49
Wound necrosis	7	8.04
Revision of amputation	7	8.04
Phantom pain	4	4.59

by Ouchemi *et al.*,[6] 50 cases for 36 months period in Malian study by Touré *et al.*,[7] 162 cases for 2 years in Tanzanian study by Chalya *et al.*,[8] and 132 cases for 5 years period in Nigerian study by Ajibade *et al.*[9] The prevalence of major limb amputation in our study was more lower than other studies. It could be explained that this result contained just all cases recensed in vascular surgical unit.

Male older was the most common risk factor for vascular disease. The predominance of male gender in major amputation of limbs in vascular surgery publications is common.[10,11] There was 82% of male in our study with 56.34 years old of average age. The predominance of male older in vascular amputation could be explained that male older is risk factor for cardiovascular disease. However, other studies showed the sex difference for the risk of amputation.[12,13] The average age of major amputation of limb published in sub-Saharan African studies was younger: 32 years in Alegbeleye,[5] 43 years in Ouchemi *et al.*,[6] 38 years in Touré *et al.*,[7] and 28 years in Chalya *et al.*[8] The predominance of youth in population undergoing major amputation of limb published in these sub-Saharan African studies could be explained by the predominance of trauma etiology. The male predominance is still observed in major amputation of limb following vascular disease or after trauma. In Western countries, there was predominance of male older in major amputation of limb performed in vascular surgery.[11,14]

If trauma and malignancies were most common indications for amputations in young adults, complications of diabetes mellitus and peripheral vascular diseases were the main indications in older patients. Peripheral arterial disease and diabetic peripheral arteriopathy are the most common cause of major amputation of limb in patients admitted in vascular surgery unit. Dysvascular disease constitutes 54% of reason of amputation in 1.6 million persons living with the loss of a limb in United States in the year 2005.[1] In study by Ubayawansa *et al.*, the most indications of the lower extremity amputation were diabetic foot ulcer (37%) and peripheral vascular disease (31%) followed by trauma (7%).[15] Peripheral arterial disease was the leading cause of the lower limb major amputation (82%) in study by da Rocha *et al.*[16] The causes of major limb amputation published in sub-Saharan African studies varied from study to study. However, there was predominance of trauma in leading cause of major amputation of limb in sub-Saharan African studies. Trauma was the leading cause of major amputation of limb in study by Alegbeleye. (60%),[5] in study by Thanni and Tade. (34%),[17] in study by Ouchemi *et al.* (47%),[6] in study by Touré *et al.* (26%),[7] in study by Ajibade *et al.*,[9] and in study by Souna *et al.*[18] Diabetic arteriopathy was the leading cause of major amputation of limb in study by Chalya *et al.* (41%).[8] In our study, diabetic gangrene (62%) was the leading cause of major amputation of limb.

Many researchers have been determined the risk factors contributing to major amputation of limb in patient presented dysvascular disease. According study by Long *et al.*, diabetes mellitus is higher risk of major amputation than minor amputation in patients with peripheral artery disease (56.5% vs. 38.2%; $P < 0.001$).[19] Diabetes mellitus is the most common risk factors of major amputation of limb, seen in over two-thirds patients undergoing major amputations secondary to dysvascular disease.[1] There was higher considerable prevalence of major amputation of limb in diabetic population than non-diabetic. The prevalence of major lower extremity amputation ranges from 0.7 to 332.4/100,000 in the diabetic population and 3.0 to 76.1/100,000 in the general population.[20] Hypertension (81%) and diabetes mellitus (79%) were the most common comorbidities in patients undergoing major lower extremity amputations in study by Chahrour *et al.*[21] In our study, the most risk factors of cardiovascular disease were male older (72.34%), high blood pressure (81.60%), diabetes mellitus (62.06%), and smoking (52.87%). Hypertension is another most common risk factor for lower extremity amputations in patients undergoing peripheral arterial disease. Recent study showed that hypertension was the leading cardiovascular risk factor (75%) for 338 major amputations due to peripheral arterial disease.[22] Smoking is considered to be a significant risk factor associated with the development of peripheral vascular disease. Smokers have more than double the risk for peripheral arterial disease compared to non-smokers.[23] There was 52% of smokers in our study.

Lower limb is the most location of major amputation of extremity. Many researchers published major amputation of the lower extremity than the upper extremity. Major amputations were more located in the lower limb (97%) than in the upper limb (2%) in our study. Our result was similar in other sub-Saharan African studies. The rate of the lower extremity amputations published in sub-Saharan African studies was 57% in study by Alegbeleye,[5] 74% in study by Ajibade *et al.*,[9] 84% in study by Ouchemi *et al.*,[6] 76% in study by Touré *et al.*,[7] 86% in study by Chalya *et al.*,[8] 75% in study by Ogundele *et al.*,[24] and 84% in Nwosu.[25] The predominance of the lower limb is still observed in other studies published in Western countries.

Major lower extremity amputation is a life-changing procedure of patients. There was an adverse social implications of and effects on the capacity to work, quality of life, and self-image are devastating. Level of the lower extremity amputation could be transfemoral (above the knee, between the knee joint and the hip joint)

or transtibial (below the knee, between the ankle joint and the knee joint). In our study, the majority of patients have been amputated below knee (55%). Level of the lower extremity amputation published in sub-Saharan study was disparate, varied among study. Major lower extremity amputation was most performed above knee in study by Nwosu *et al.* (42%),[25] by Alegbeleye (33%),[5] and by Touré *et al.* (34%).[7] However, major lower extremity amputation was most performed below knee in study by Ogundele *et al.* (45%),[24] by Ajibade *et al.* (36%),[9] by Ouchemi *et al.* (50%),[6] and by Chalya *et al.* (46%).[8] In Western countries, level of amputation was most performed below knee in study by Aulivola *et al.* (73%)[26] and by Ploeg *et al.* (55%).[27] Some researchers have been determined outcomes of major lower extremity amputation following level of amputation. The study by Ploeg *et al.* showed higher risk of wound infection in below knee amputations (10%) than above knee amputations but above knee amputations have higher risk of hospital mortality than above knee amputations (17.8% vs. 9.1%).[27] Furthermore, transtibial amputation was an independent factors reducing mortality in study by Ambler *et al.* ($P < 0.001$).[28]

In recent years, there has been an increasing interest in outcomes of major amputation of limb following type of anesthesia. The use of general anesthesia versus regional anesthesia for performing major lower extremity amputation is an area of ongoing debate. In our study, amputations were more performed using regional anesthesia (72%) than general anesthesia (17%). The study by Moreira *et al.* concluded that there is not significant effect on perioperative outcomes after major lower extremity amputation in the functionally impaired geriatric population according mode of anesthesia.[29] Other study showed too no difference in outcomes between regional or general anesthesia techniques in patients undergoing lower extremity amputation.[30,31]

A number of researchers have reported the outcomes of major amputation of limb. There were many studies published the results of major amputation of limb in sub-Saharan African study. In sub-Saharan African studies, the hospital mortality rates varied from study to study: 8% in study by Touré *et al.*,[7] 16% in study by Chalya *et al.*,[8] 15% in study by Ouchemi *et al.*,[6] and 2% in study by Ajibade *et al.*[9] The mortality rate was 6% in our study. The truth mortality rate of major amputation of limbs in sub-Saharan African countries remain unknown because these studies have been recensed the hospital mortality rate at a single teaching hospital. In Western countries, the mortality rate after major amputation of limbs was decreased from 19.8% in 2005 to 17.4% in 2015 in Germany,[32] 10% in Spain.[33] However, there is an increasing of mortality rate in years following major amputation of limb. This hypothesis has been demonstrated by others researchers. According study by Stern *et al.*, the overall mortality rate after lower extremity amputation was, respectively, 47%, 61%, 70%, and 62% at 1, 2, 3, and 5-year following major amputation.[34] Mortality rate varied, respectively, 33% and 65% at 1 and 4 years after major lower extremity amputation in recent Italian study by Cascini *et al.*[35]

Limitations

There are limitations in this study that could be addressed in the future research. First, the study focused on all cases of major amputation of limb recensed in Vascular Surgical Unit. Hence, the frequency of major amputation of limb in this study could not represent the truth prevalence of major amputation of limb in this hospital center because all cases due to trauma in Orthopedic Traumatology Unit do not include in this study.

CONCLUSION

Diabetic gangrene and peripheral arterial disease were the most common surgical indications of major limb amputation. Early detection and management of diabetes mellitus and other cardiovascular risk factors are more important to prevent risk of amputation.

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Original Article

Magnetic Resonance Imaging Evaluation of the Brain in Children with Developmental Delay

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Abstract

Background: Global developmental delay is an umbrella term used when children are significantly delayed in their cognitive and physical development. There is usually a specific condition that causes this delay. However, it is sometimes difficult to spot this underlying condition. Magnetic resonance imaging (MRI) brain helps to diagnose or to rule out such conditions.

Aim and Objective: The objectives of the study are as follows: (1) To categorize the morphological abnormalities in brain MRI and to determine the prevalence of developmental delay in children. (2) To detect the proportion of normal MRI in children with developmental delay.

Materials and Methods: It is an observational and prospective MRI brain study of 100 pediatric patients done in the radiology department of the tertiary care center for 2 years (October 2020–December 2021).

Results: The majority of the children (36%) were in the age group of 4–6 years. There was male predominance (62%). The prevalence of abnormal MRI findings was 76% in our study. Forty-eight (63.3%) children had findings consistent with neurovascular diseases while 13 (17.1%) and 9 (11.8%) children had congenital and developmental disorders and non-specific imaging findings, respectively. Neoplastic and cystic lesions and multifactorial etiology were noted in 4 (5.2%) and 2 (2.6%) children, respectively. There was a significant association between clinical findings and MRI findings as per the Chi-square test ($P < 0.05$).

Conclusion: The various morphological appearances of developmental delay on MRI and further categorizing them into various subgroups paving way for treating clinicians to plan proper management and parent counseling. The most common cause for the development delay was found to be neurovascular disease.

Key words: Developmental delay, Diffusion weighted imaging, Magnetic resonance imaging, T1W, T2W image

INTRODUCTION

Global developmental delay (GDD) is diagnosed when a child is delayed in one or more milestones, categorized into motor skills, speech, cognitive skills, and social and emotional development.[1] There is usually a specific condition that causes this delay, such as Fragile X syndrome or other chromosomal abnormalities. However, it is sometimes difficult to spot this underlying condition.[2]

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The degree of developmental delay is often further classified as mild (functional age <33% below chronological age), moderate (functional age 34–66% of chronological age), and severe (functional age <66% of chronological age).[3] A significant delay is defined as performance that is two or more standard deviations below the mean on age-appropriate standardized norm-referenced testing (usually conducted in secondary or tertiary care settings).[4] A significant delay in two or more developmental domains affecting children under the age of 5 years is termed GDD.[5]

From a pathophysiological point of view, developmental delay is the result of interference with the normal development of the brain. This interference may occur at a number of different stages in the embryology and/or postnatal development of the brain, affecting the formation of the brain or any of the processes regulating functional

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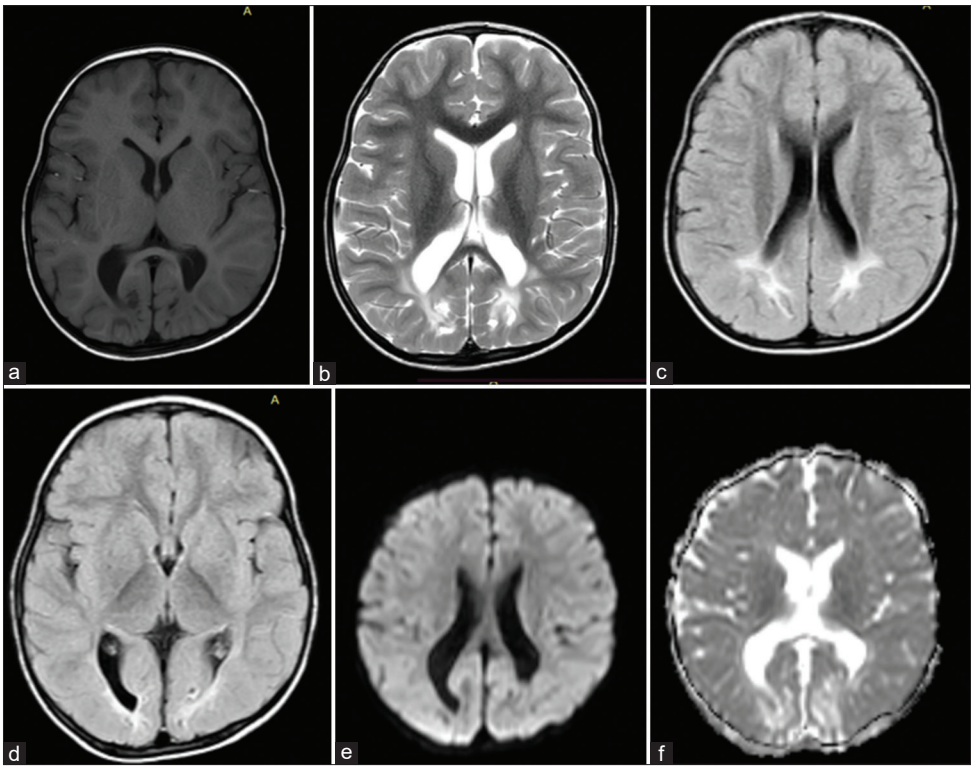


Figure 1: Birth Hypoxic ischemic insult. Ill-defined axial T2 and FLAIR (b-d) hyperintensity in subcortical and deep white matter of bilateral occipital and posterior parietal lobes, appearing hypointense on axial T1 (a), showing no restriction on DWI (e) and increased ADC (f) value, associated with white matter volume loss causing prominence of occipital horns of bilateral lateral ventricles

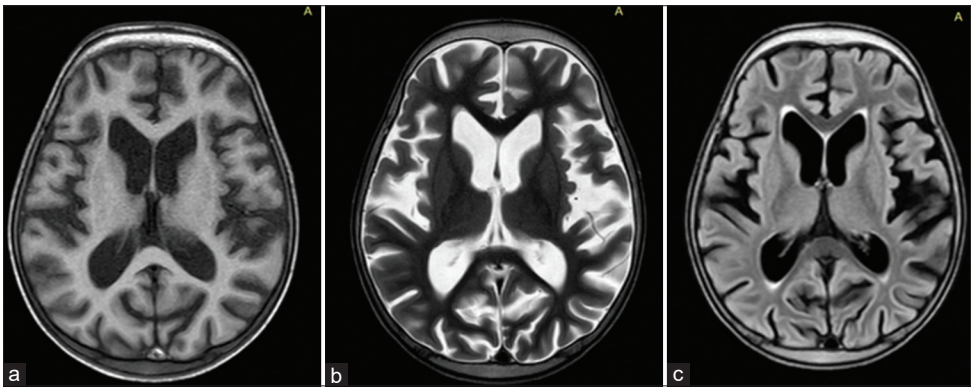


Figure 2: Predominant white matter loss. Axial T1W, T2W, and FLAIR images demonstrate diffuse mild dilatation of supra-tentorial CSF sulcal spaces and ventricular systems associated with mild diffuse white matter volume loss s/o cerebral atrophy-predominantly white matter

development (myelination, neuronal selection, and programmed cell death), which mainly occurs after birth.[6] There are various methods and tests to evaluate development. The best test is the Denver development screening test and its modified form is the Denver development screening test II.[7]

Careful evaluation and investigation can reveal a cause in 50–70% cases[8] with developmental delay this wide variation [Graph 1] could be attributed to patient selection criteria where high proportions are reported; some of the reported abnormalities are in children where diagnosis would be obvious clinically.[9] Brain magnetic resonance imaging (MRI) is one of the major investigations of these patients. Based on the previous studies, about 60% of cases have abnormal brain MRI.[10]

Neurologically, once the child is brought for a developmental delay concern, a delayed developmental status should be assumed unless the evaluation suggests otherwise.[11] If developmental delays are detected late, and opportunities for early intervention are lost, resulting in poor outcomes such as learning difficulties, behavior problems, and functional

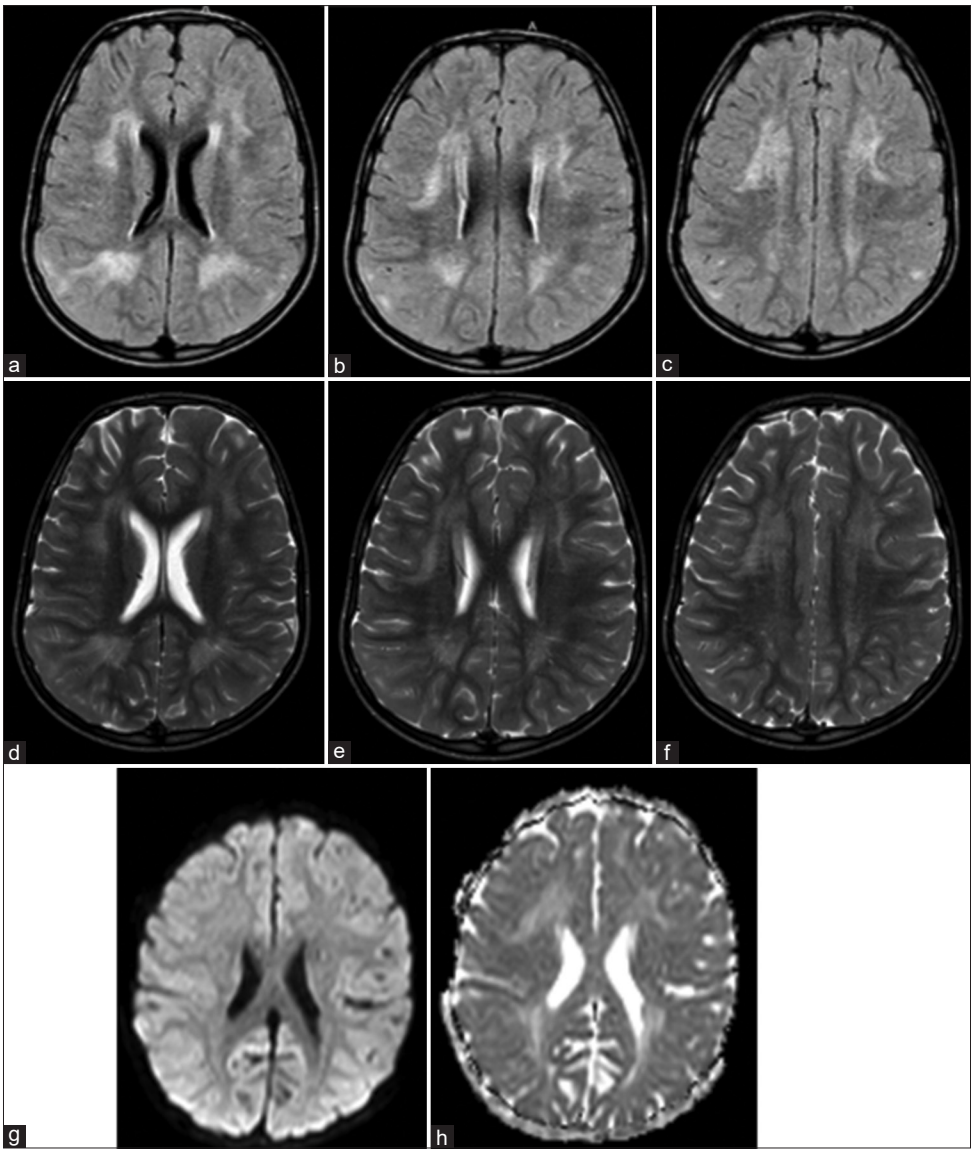


Figure 3: Metachromatic leukodystrophy. Bilaterally symmetrical axial FLAIR and T2W Hyperintensities (a-c, e-g) in bilateral periventricular and subcortical white matter of bilateral frontal and parietal lobes giving butterfly pattern with sparing of subcortical U fibers. On axial T2W images, perivenular sparing is seen giving tigroid like pattern. DWI (g) demonstrates no restricted diffusion associated with increased ADC (h) value

impairments later on in life.[12] There is strong research evidence suggesting that effective early identification of developmental delays and timely early intervention can positively alter a child's long-term trajectory.[13] Hence, the present study was done at our tertiary care center to categorize the morphological abnormalities in brain MRI and to determine the prevalence of the developmental delay in children.

OBSERVATIONS AND RESULTS

A hospital-based observational and prospective study was conducted among 100 children to categorize the morphological abnormalities in brain MRI and to determine the prevalence of developmental delay in children.

The majority of the children (36%) were in the age group of 4–6 years followed by 31 (31%) children in the age group of 7–9 years, 22 (22%) children in the age group of 2–3 years and 8 (8%) children in the 10–12 years of age. The mean age of the children was 5.79 ± 2.58 years. There was male predominance (62%) whereas female children constituted 38% of the study group. 27 (27%) children were term while 41 (41%) and 32 (32%) children were preterm and late-term, respectively.

Forty-three (43%) children presented with developmental delay had seizures as the main complaint, while 19 (19%) and 7 (7%) children had other neurological deficits and respiratory and cardiac disease, respectively. Four (4%) children had

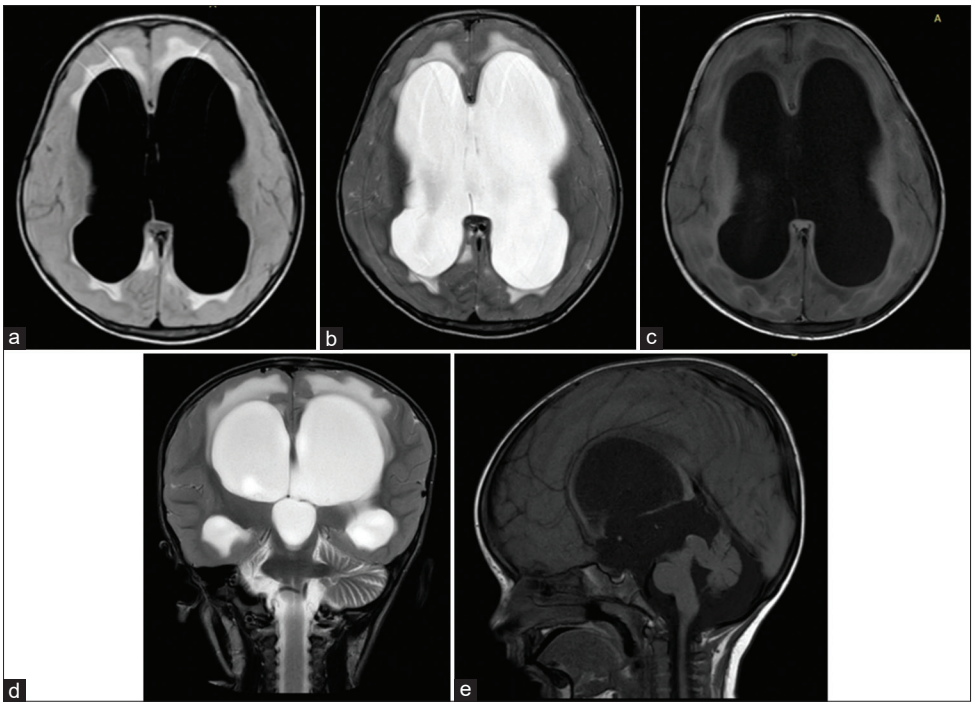


Figure 4: Non-communicating hydrocephalus. Axial FLAIR, T2w and T1w (a-c), coronal T2W, and sagittal T1w images demonstrate grossly dilated bilateral lateral ventricles and third ventricle (Right lateral ventricle measuring 3 cm, left lateral measuring 3.56 cm and third ventricle measuring 2.6 cm) with blunting of gyri and effacement of CSF sulcal spaces of bilateral cerebral hemispheres secondary to aqueductal stenosis at the level of midbrain. Increased T2W and FLAIR signal intensity is seen surrounding bilateral lateral ventricle s/o periventricular CSF ooze. Fourth ventricle appears prominent measuring 8 mm

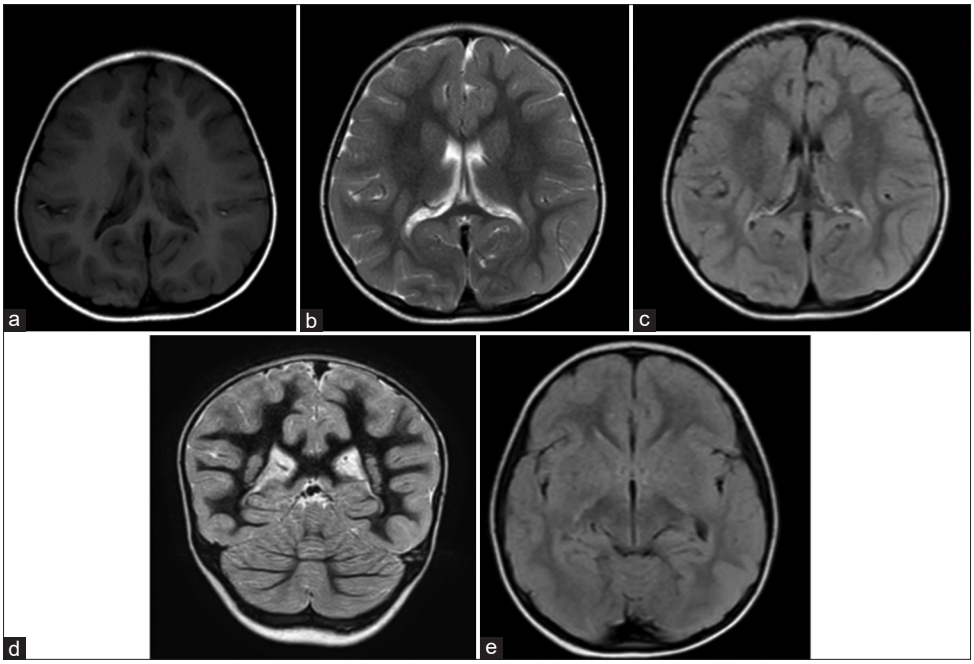


Figure 5: Migrational disorder. There is gray matter like signal intensity area in bilateral parietal periventricular region appearing hypointense on axial T1W (a), isointense on axial T2W (b), FLAIR (c), and coronal T1W-IR images s/o heterotopia (band like). Paucity of sulcations in bilateral cerebral hemispheres.

hypothyroidism. Five (5%) children had associated features such as visual disturbances and reduced head circumference. No significant clinical association was demonstrated in 22 (22%) children.

Among the children with neurological deficits (19%), 9 (47.3%) children had hypotonia while 6 (31.6%) and 3 (15.8%) children had spasticity and gait abnormalities, respectively. One (5.3%) child had hemiplegic cerebral palsy [Table 1].

Table 1: Distribution of children according to prevalence of neurological deficits

Neurological deficits	*N*	%
Hypotonia	9	47.3
Spasticity	6	31.6
Gait abnormality	3	15.8
Hemiplegic cerebral palsy	1	5.3
Total	19	100

Table 2: Distribution of children according to abnormal MRI findings (*n*=76)

Abnormal MRI Findings	*N*	%
Neurovascular	48	63.3
Congenital and Developmental	13	17.1
Non-specific imaging findings	9	11.8
Neoplastic and cystic lesions	4	5.2
Multifactorial	2	2.6
Total	76	100

MRI: Magnetic resonance imaging

Table 3: Distribution of children according to involved brain structures

Involved Brain Structures	MRI findings			
	Normal		Abnormal	
	n	%	*N*	%
White Matter	48	48	52	52
Ventricles	62	62	38	38
Corpus callosum	77	77	23	23
Gray matter	89	89	11	11
Basal ganglia	94	94	6	6
Cranial vault	95	95	5	5
Limbic system	97	97	3	3
Brain stem	97	97	3	3
Others	91	91	9	9

MRI: Magnetic resonance imaging

Table 4: Association of Clinical Findings and MRI findings of children

Clinical findings	MRI findings				Total	*P*-value
	Normal		Abnormal			
	n	%	*n*	%		
Only developmental delay	12	12	10	10	22	<0.05
Developmental delay plus	12	12	66	66	78	
Total	24	24	76	76	100	

MRI: Magnetic resonance imaging

The prevalence of abnormal MRI findings was 76%in our study [Graph 1]. On MRI, 48 (63.3%) children had findings consistent with neurovascular diseases while 13 (17.1%) and 9 (11.8%) children had congenital and developmental disorders and non-specific imaging findings, respectively. Neoplastic and cystic lesions and multifactorial etiology were noted in 4 (5.2%) and 2 (2.6%) children, respectively [Table 2].

Our study noted the white matter and ventricular [Figures 1, 2 and 3] abnormalities in 52 (52%) and 38 (38%) children [Figure 4] with developmental delay, respectively. The corpus callosum was abnormal in 23 (23%) children while the gray matter [Figure 5] showed abnormalities in 11 (11%) children. Abnormalities of the basal ganglia and cranial vault were seen in 6 (6%) and 5 (5%) children, respectively. The limbic system and brain stem abnormalities were seen in 3 (3%) children each. Around 9 (9%) of children had involvement of other brain structures such as vermis, cerebellar tonsils, subarachnoid spaces and cisterns, and choroid plexus [Figure 6, Graph 2 and Table 3].

Out of 43 (43%) developmentally delayed children associated with seizures, 40 (40%) children had abnormal MRI. Further, it was noted that among 24 (24%) children with normal MRI only 3 (3%) children were associated with seizures [Graph 3].

Among 22 (22%) children presenting with "only" developmental delay, 12 (12%) children had normal MRI findings. Out of 78 (78%), children presented with additional clinical features along with developmental delay, 66 (66%) children had abnormal MRI. There was a significant association between clinical findings and MRI findings as per the Chi-square test ($P < 0.05$).

METHODOLOGY

The study was conducted among 100 children to categorize the morphological abnormalities in brain MRI and to determine the prevalence of developmental delay in children.

Study Design Duration

A hospital-based observational and prospective study was done in 2 years.

Study Area

The study was done at a tertiary care center in the department of radiodiagnosis on attending outpatient department/inpatient department.

Study Population

All children between 2 years and 12 years of age with a history of developmental delay were referred from the pediatric department at our tertiary care enter who fulfilled the inclusion criteria.

Sample Size

The sample size was 100 patients.

Inclusion and Exclusion Criteria

2–12 years of children with a history of development delay referred from the pediatric department are included in the

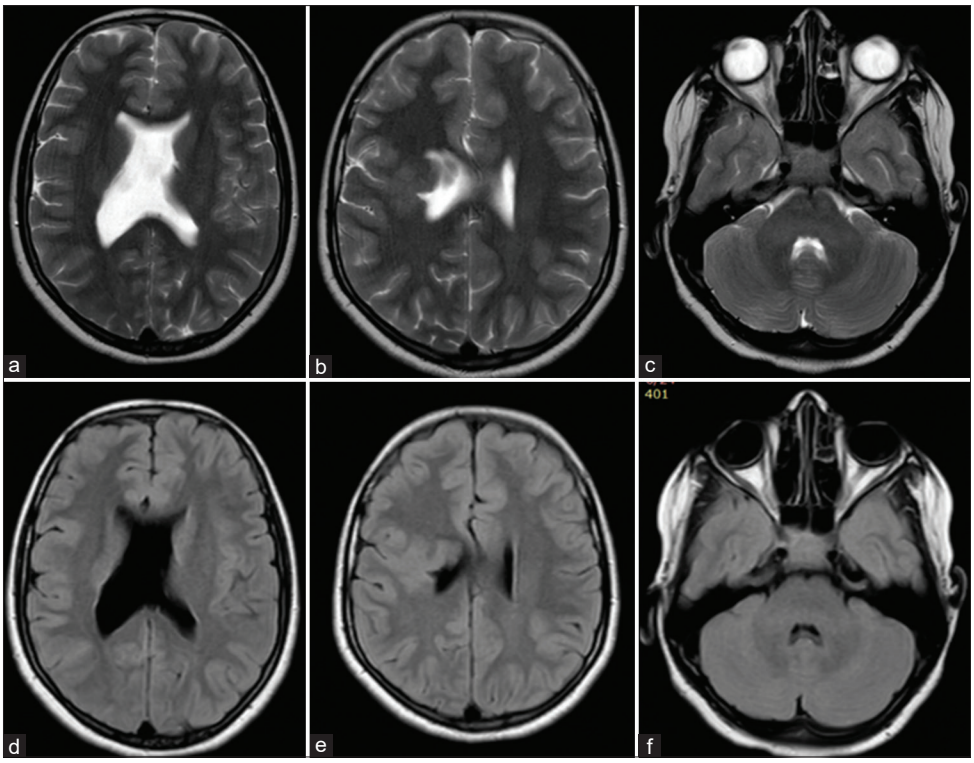
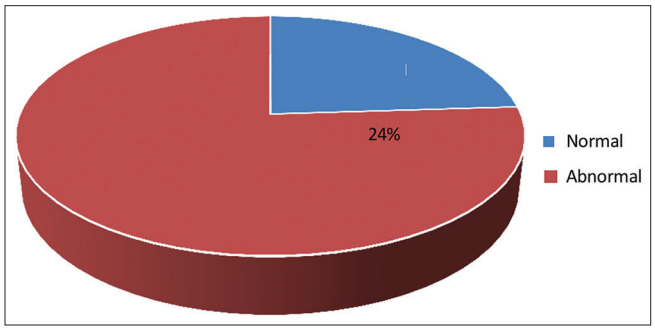
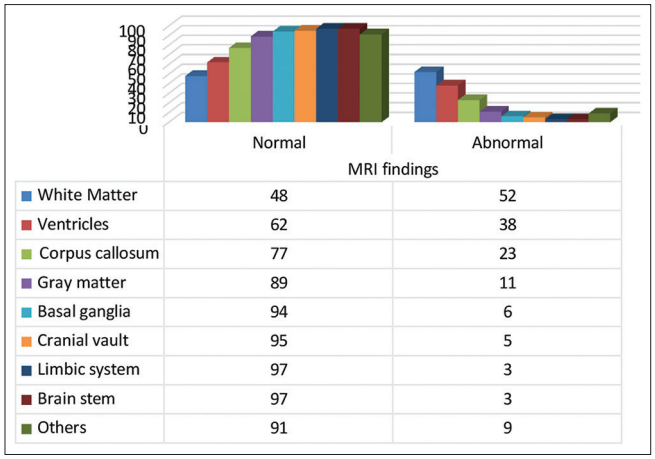


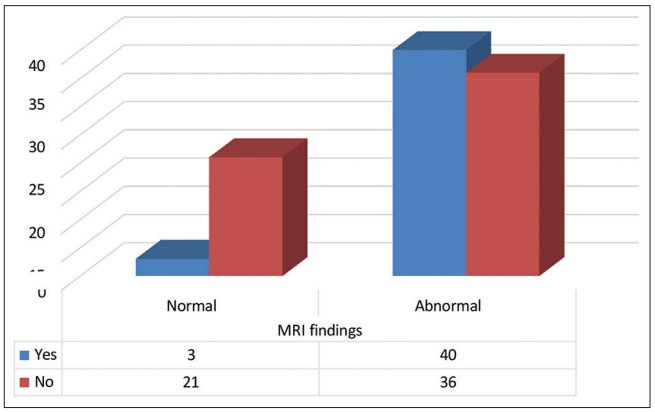
Figure 6: Septo-optic dysplasia. Axial T2 (a-c) and FLAIR (c-e) demonstrates absent septum pellucidum. Nodular grey matter heterotopia in subependymal and subcortical region of right frontoparietal lobes. Polymicrogyria noted in right frontoparietal region. Grey matter lined CSF cleft is noted in right frontoparietal region with dimpling on lateral wall of the right lateral ventricle s/o closed lip schizencephaly. Hypoplastic right optic nerve is noted



Graph 1: Distribution of children according to Magnetic resonance imaging Findings



Graph 2: Distribution of children according to involved brain structures



Graph 3: Association of seizures and magnetic resonance imaging findings of children

study. Patients with contraindications to MRI such as metallic body implants and artificial heart valves, patients with acute infections such as tonsillitis and pneumonia, andchildren with a known genetic disorder such as Downs and Turner syndromes are excluded from the study.

Methods

The study was done at our tertiary care center in the department of radiodiagnosis. Informed consent was taken in writing from the patient's attendant. Infants were examined and sedated with IV drugs under the consent and

presence of the pediatrician using anesthetic drugs by the anesthetist in their presence. MRI brain was done by MRI machine of power 1.5 Tesla of Philips which was available at our tertiary care center. The sequences used were: Axial T1, T2, and FLAIR images, Coronal T2W, Sagittal T1W, GRE, and inversion recovery images, DW1, and ADC maps.

DISCUSSION

A hospital-based observational and prospective study was conducted among 100 children to categorize the morphological [Table 4] abnormalities in brain MRI and to determine the prevalence of developmental delay in children. In India, sources have found the prevalence of 1.5–2.5% of developmental delay in children under 2 years of age.[14] These impairments impact not only the child and the family, but also society, in terms of the cost of providing health care, educational support, and treatment services.[15] Evidence supports that early treatment of developmental disorders leads to improved outcomes for children and reduced costs to society.[16]

In the present study, the majority of the children (36%) were in the age group of 4– 6 years followed by 31 (31%) children in the age group of 7–9 years, 22 (22%) children in the age group of 2–3 years, and 8 (8%) children in the 10–12 years of age. The mean age of the children was 5.79 ± 2.58 years. There was male predominance (62%) whereas female children constituted 38% of the study group. There was no significant difference in the mean age of male and female children as per the Student's *t*-test ($P > 0.05$). This is similar to the studies of Elanchezhian and Kalaivani.[17] and Ali *et al*.[18]

It was observed in the present study that among the children with neurological deficits (19%), 9 (47.3%) children had hypotonia while 6 (31.6%) and 3 (15.8%) children had spasticity and gait abnormalities, respectively. One (5.3%) child had hemiplegic cerebral palsy. The prevalence of abnormal MRI findings was 76%in our study. This is concordant to the studies of Elanchezhian and Kalaivani[17] Bouhadiba *et al*.,[19] Moon *et al*.,[20] Momen *et al*.,[21] Habibullah *et al*.,[22] and Kalaiarasan *et al*.[23]

It was observed in our study that 48 (63.3%) children had findings consistent with neurovascular diseases while 13 (17.1%) and 9 (11.8%) children had congenital and developmental disorders and nonspecific imaging findings, respectively. Neoplastic and cystic lesions and multifactorial etiology were noted in 4 (5.2%) and 2 (2.6%) children, respectively. This is consistent with the studies of Elanchezhian and Kalaivani[17] Ali *et al*.[18]

In the present study, 15 (15%) and 35 (35%) children in the age group of 2–3 years and 4–6 years, respectively, had abnormal brain MRI findings while 21 (21%) and 5 (5%) children in the age group of 7–9 years and 10–12 years, respectively, had abnormal brain MRI findings. There was a significant association between age and MRI findings of children as per the Chi-square test ($P < 0.05$). Habibullah *et al*.[22] noted similar observations in their study.

It was observed in our study that among 22 (22%) children presenting with "only" developmental delay, 12 (12%) children had normal MRI findings. Out of 78 (78%), children presented with additional clinical features along with developmental delay, 66 (66%) children had abnormal MRI. There was a significant association between clinical findings and MRI findings as the per Chi-square test ($P < 0.05$). Similar observations were noted in the studies of Habibullah *et al*.[22] and Ali *et al*.[18]

CONCLUSION

The most common cause of developmental delay is neurovascular pathologies predominantly affecting white matter and the ventricular system. MRI is the only modality for diagnosis. MRI is safe for children as it has no ionizing radiation. MRI helps in the early identification of causes for developmental delay and, therefore, early intervention will be possible, which is going to prevent long-term insults and detrimental consequences.

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Original Article

Perioperative Anaesthetic Management in Revision Total Hip Arthroplasties in a Tertiary Care Hospital

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Abstract

Background: The revision total hip arthroplasties are associated with significant perioperative mortality and morbidity which can be due to patient factors, surgical factors, and anaesthetic factors. The objective of this study is to audit the common anaesthesia practices in the revision total hip arthroplasties in the perioperative period.

Materials and Methods: A total of 39 patients who underwent revision total hip arthroplasty in a period of 2 years participated in the prospective observational study. The pre-operative, intraoperative, and post-operative data were assessed using a case record form and analyzed using a statistical software.

Results: There were 26 males (66.7%) and 13 females (33.33%). The mean age was 56.12 years (Range 23–81, SD = 15.21). Hypertension was the most common comorbidity among the study subjects. Regional anaesthesia was preferred to general anaesthesia (15.38%). The mean blood loss during the surgery was 778.2 mL. Twenty patients (51%) required blood transfusion. The patients who received tranexamic acid had lesser blood loss compared to those who had not received tranexamic acid. Thirty-seven patients (94.87%) recovered uneventfully.

Conclusion: The role of tranexamic acid in the improvement of perioperative outcome and reduction of the need for allogeneic blood transfusion is again confirmed by the study. The usage of neuraxial techniques over general anaesthesia is associated with almost similar perioperative outcomes. These findings suggest that the decision of anaesthetic technique should depend on the patient, surgical and anaesthetic risks of morbidity and mortality.

Key words: Blood loss, Blood transfusion, Regional anaesthesia, Total hip arthroplasties, Tranexamic acid

INTRODUCTION

The first recorded hip replacement surgery was attempted as early as in 1891 by Themistocles Gluck (1853–1942) in Germany.[1] With the advancements in both the surgical as well as the anaesthetic techniques, the joint arthroplasties have come a long way to improve the quality of life especially in elderly population. With the increasing count of primary hip arthroplasties happening, the number of revision surgeries tend to increase in manifold.

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The revision total hip arthroplasties are associated with significant perioperative mortality and morbidity which can be due to patient factors, surgical factors, and anaesthetic factors. The identification of such factors can help in optimizing the perioperative outcome and might help in reducing the impact on the cost of medical care.[2]

The aim of this study was to identify the common anaesthesia practices in the revision total hip arthroplasties. The primary objectives were to study the common anaesthesia techniques, associated blood loss, blood and blood products used, haemodynamic stability, and post-operative recovery of the patient. The secondary

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objectives were to study the common pain relief practices, demographic and statistical data affecting the outcomes, and any anaesthesia-related complications.

MATERIALS AND METHODS

Study Design

This study was prospective observational study.

Inclusion Criteria

The following criteria were included in the study:

1. All the patients who underwent revision total hip joint replacement surgery during the period of study.
2. All the patients above 18 years of age and were willing to participate in the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. All the patients who were not willing to participate in the study.

Study Procedure

This study was conducted in the elective orthopedic operation theaters in a tertiary care hospital for 2 years after the Institutional Ethics Committee approval. Universal sampling method was used and all patients fulfilling the inclusion and exclusion criteria were included in the study and the informed consent was taken after doing the pre-operative assessment.

Data Collection

The pre-operative, intraoperative, and post-operative records of all patients undergoing the revision total hip arthroplasties were collected and an appropriate case record form was developed. The following details were collected from each patient's form.

1. Demographic data: Name, age, sex, weight, height, body mass index, diagnosis, medical history, previous surgery history, medications, addictions, relevant pre-operative investigations, and American Society of Anaesthesiologists (ASA) status of the patient.
2. Anaesthesia techniques: General anaesthesia (GA), regional anaesthesia (RA – spinal/epidural/block), combined GA and RA.
3. Intraoperative haemodynamics: Pulse rate, blood pressure, SpO_2, $EtCO_2$, and Respiratory rate.
4. Fluid, blood and blood products:
   a) Intraoperative usage of crystalloids, colloids, and blood and blood products.
   b) Need for inotropic supports.
      - Inj. Noradrenaline 0.01–0.02 μ/kg/min was started as first choice as a routine practice.
   c) Blood loss.
   d) Use of Inj.Tranexamic acid.
5. Pain management
   - Type of technique used – IV drugs/Epidural boluses/Continuous epidural infusions/Blocks/Local Infiltration/other method
   - As per institutional protocol, Inj. Paracetamol 1g 6 h was given to all patients. Inj. Tramadol 50–100 mg 8 h was given on demand basis in the first 24 h postoperatively.
   - Epidural boluses of Inj. Bupivacaine 0.125 –0.25% 5cc are given with or without Inj. Buprenorphine 30–90μ if epidural catheter *in situ*.
   - Local infiltration Analgesia given by surgeons' intraoperatively. The routine practice was to give Inj. Bupivacaine 0.5% 2 mg/kg + Inj. Clonidine 1 μ/kg + Inj. Fentanyl 1–2 μ/kg.
6. Post-operative recovery.

Statistical Analysis

- The data were entered in Microsoft Excel sheet and analyzed using SPSS version 25 and EPI Info version 7.3.
- Chi-square test was used to assess the association between categorical variables.
- Comparison of categorical variables was done using counts and percentages.
- Mean and standard variations was used for continuous variables.
- $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 39 patients were assessed and included in the study. The data were sorted manually and entered into a Microsoft Excel Sheet and analyzed using statistical software.

Patient Demographics

- There were 26 (66.67%) males and 13 (33.33%) females. The mean age was 56.12 ± 15.21 years (range 23–81, standard deviation = 15.21). The majority of the patients were ASA II followed by ASA I [Table 1].
- Fifteen patients had no comorbidities. Fourteen had hypertension, followed by stroke in four patients. There were three patients of diabetes mellitus, ischemic heart disease, and old pulmonary koch's each.
- Eighteen (46.15%) patients had one previous surgery followed by 13 (33.33%) patients with two previous hip surgeries. Three previous hip surgeries were done in 5 (12.82%) patients.
- [Table 2] 15 (38.46%) patients were given Subarachnoid Block (SAB) followed by combined spinal epidural

Table 1: Patient demographics and pre-operative data

Demographic	Variable	Number (%)
Gender, n (%)	Female	13 (33.33)
	Male	26 (66.67)
Age (years)	Mean	56.12 years
	Range	23–81
	Standard deviation	15.21
ASA grading, n (%)	I	14 (35.90)
	II	23 (58.97)
	III	2 (5.13)
	IV	0 (0)
Co-morbidities, n	No comorbidities	15
	Hypertension	14
	Stroke	4
	Diabetes mellitus	3
	Ischemic heart disease	3
	Old Pulmonary Koch's	3
	Ankylosing spondylosis	2
	Retroviral disease	2
Pre-operative anaemia (as per WHO classification)	Males	23 (88.46)
	Females	12 (92.31)
Number of previous hip surgeries, n (%)	1	18 (46.15)
	2	13 (33.33)
	3	5 (12.82)
	4	1 (2.56)
	5	1 (2.56)
	6	1 (2.56)

Table 2: Type of anaesthesia technique employed

Type of anesthesia	Number	Percentage
CSE	10	25.64
GA	05	12.82
SAB	15	38.46
SAB+EA	08	20.51
GA+EA	01	2.56
Total	39	100

anaesthesia (CSE) given to 10 (25.64%) patients. Subarachnoid block and epidural anaesthesia (SAB + EA) was given at different levels in 8 (20.51%) patients. General anaesthesia (GA) was given in 06 (15.38%) patients [Table 3].

- [Figure 1] 20 (51.28%) patients were operated within 2.1–4 h followed by 13 (33.33%) patients in more than 4 h. Only 6 (15.38%) patients were operated between 1 and 2 h.
- Among 39 patients, 25 (64.10%) patients lost blood between 501 and 1000 mL during surgery followed by 8 (20.51%) patients who lost 1001–1500 mL blood during surgery.
- [Figure 2] 19 (49%) patients were not transfused during surgery followed by 9 (23%) patients that were transfused 1–250 mL blood and 9 (23%) patients were transfused 251–500 mL blood during surgery. Only 2 (5%) patients were given more than 500 mL.

Table 3: Intraoperative data

Data	Variable	Number (%)
Duration of surgery (hours)	1–2 h	06 (15.38)
	2.1–4 h	20 (51.28)
	>4 h	13 (33.33)
	Mean duration	212.5 min
Invasive monitoring during surgery (arterial/central venous line)	Yes	02 (5.13)
	No	37 (94.87)
Blood loss during surgery (mL)	≤500 mL	06 (15.38)
	501–1000 mL	25 (64.10)
	1001–1500 mL	08 (20.51)
	Mean blood loss	778.2 mL
Blood transfusion during surgery (mL)	No Transfusion	19 (49)
	1–250 mL	09 (23)
	251–500 mL	09 (23)
	>500 mL	02 (5)
	Mean blood transfusion	163.4 mL
Crystalloids given during surgery (mL)	<1000 mL	09 (23.08)
	1000–1500 mL	27 (69.23)
	>1500 mL	03 (7.69)
	Mean crystalloids given	1139.2 mL
Colloids given during surgery (ml)	Not given	16 (41.02)
	1–250 mL	04 (10.26)
	251–500 mL	19 (48.72)
	Mean colloids given	252.2 mL
Inotropes used during surgery	Yes	06 (15.38)
	No	33 (84.62)

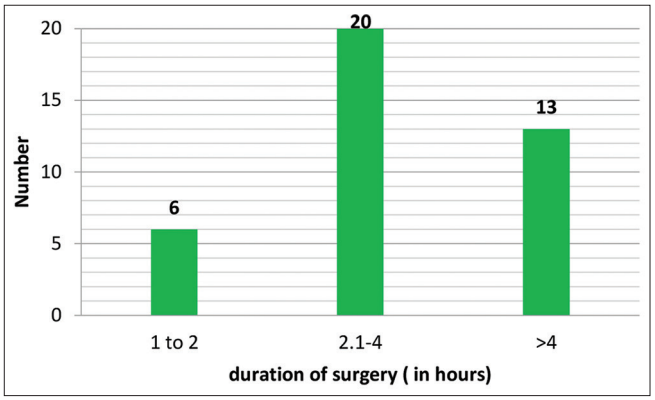

Figure 1: The distribution of study subjects according to the duration of surgery

- [Table 4] When the association of blood loss and tranexamic acid usage during surgery was seen using Chi-square test, it was found to be statistically significant ($P = 0.04$). Out of six patients having blood loss of <500 mL, all 6 (100%) patients were given tranexamic acid. Out of 25 patients having blood loss of 501–1000 mL, majority 17 (68%) patients were given tranexamic acid. Out of eight patients having blood loss of 1001–1500 mL, 5 (62.50%) patients were not given tranexamic acid.
- [Table 5] For the post-operative analgesia, 22 (56.41%) patients were given intravenous analgesia postoperatively followed by 17 (43.59%) were given

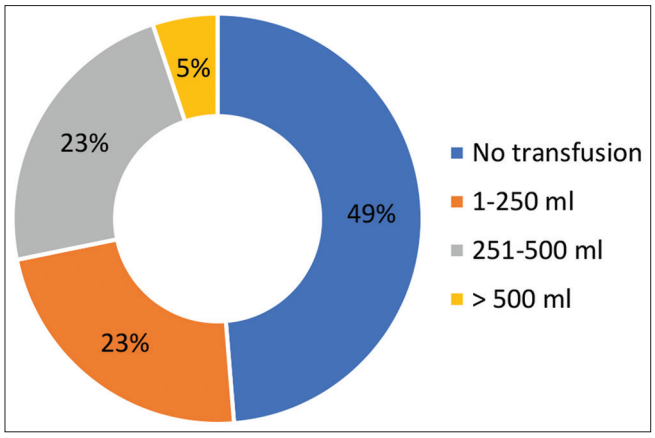

Figure 2: The distribution of study subjects according to blood transfusion during surgery

Table 4: The distribution of study subjects according to blood loss and tranexamic acid given during surgery

Tranexamic acid given	Blood loss during surgery			*P* value
	≤500 mL Number (%)	501-1000 mL Number (%)	1001-1500 mL Number (%)	
Yes	06 (100)	17 (68.00)	03 (37.50)	0.04*
No	00 (00)	08 (32.00)	05 (62.50)	
Total	06 (100)	25 (100)	08 (100)	

Table 5: Post-operative data

Data	Variable	Number (%)
Recovery after surgery	Recovery uneventful	37 (94.87)
	Intensive care unit	02 (5.13)
Pain management	Local Infiltration Analgesia	28 (71.79)
	Intravenous route	22 (56.41)
	Epidural+Intravenous route	17 (43.59)

both epidural analgesia and intravenous analgesia for pain management. Local infiltration analgesia was given by surgeons' in 28 patients (71.79%).

- 37 (94.87%) patients recovered uneventfully and only 2 (5.13%) patients were in ICU for recovery. When Chi-square test was applied to see the association between age and recovery during surgery, it was not found to be statistically significant ($P = 0.8$) [Table 6].
- [Table 7] Multivariate analyses of general anaesthesia versus neuraxial anaesthesia.
- When the association was established between age of the patient and the blood loss during surgery using the Chi-square test, it was not found to be statistically significant.

DISCUSSION

Anaesthesia management in the revision total hip arthroplasties has always been associated with significant perioperative mortality and morbidity due to elderly population and related comorbidities, prolonged surgical time, positioning, significant hemodynamic changes, perioperative blood loss, blood transfusion, postoperative complications, extended hospital stay, and anaesthetic alterations for the same.[3,4] Proper pre-operative assessment, risk stratification, and necessary pre-operative optimization with proper anaesthetic planning for stable intraoperative management and post-operative monitoring form the major components in the management of these patients.

- In our study, among the 39 patients, majority 10 (25.64%) patients were in age group of 51–60 years followed by 9 (23.08%) in age group of 61–70 years. The mean age was 56.12 ± 15.21 years (range 23–81). As per hospital episode statistics (HES) for England,[5] mean age of the patients undergoing revision surgeries was 71.8 years, whereas for the primary surgeries was 68.6 years. As per Australian National Registry,[6] the mean age of first revision is 71.4 years.
- It was found that there were 26 (66.67%) males and 13 (33.33%) females in the study. As per HES for England[5], the female rates were higher than males in the age group of 50 years and above. Traven *et al.* found that there were 54.6% females and 45.4% males who underwent revision total hip arthroplasties.[4]
- The majority of the patients were ASA II (58.97%) followed by ASA I (35.90%). Begun *et al.* found that more than 80% of the patients were healthy or had mild systemic disease (ASA 1-2) at the date of surgery.[7] Traven *et al.* found that 1.8% belonged to ASA 1, 39.7% to ASA 2, 53% to ASA 3, and 5.5% to ASA 4 among 13,948 patients who underwent revision total hip arthroplasties.[4]
- In our study, Central Neuraxial Blockade (CNB) was preferred to general anaesthesia (15.38%). Awake fiber-optic intubation was done in two patients with ankylosing spondylosis. Memtsoudis *et al.* found that in a large study of total arthroplasties from 2006 to 2010, 74.8% surgeries were performed under general anaesthesia.[8] O'Hara DA *et al.* found in a study of 9425 elderly patients for hip surgeries, General anaesthesia was used in 6206 (65%) patients and regional anaesthesia in 3219 patients.[9] Although GA was preferred in many Western literature, CNB was preferred in our institute in view of multiple factors like most of the study population undergoing arthroplasties were elderly patients and their age related comorbidities, to avoid multi-drug therapy, to reduce the opioids usage, to reduce post-operative nausea and vomiting, to encourage early feeding, early mobilization, and early recovery, and to avoid post-anaesthesia care unit stay, better post-operative pain management, and better compliability of the Indian patients.[8,10-14]
- GA was preferred in patients with active cardiac conditions, difficult spine, anticipated higher blood

Table 6: The distribution of study subjects according to age and recovery after surgery

Recovery	Age group(in years)						*P* value
	21–30 years Number (%)	31–40 years Number (%)	41–50 years Number (%)	51–60 years Number (%)	61–70 years Number (%)	>70 years Number (%)	
ICU	0 (00)	0 (00)	0 (00)	01 (10.00)	0 (00)	01 (14.25)	0.8
Recovery uneventful	03 (100)	05 (100)	05 (100)	09 (90.00)	09 (100)	06 (86.75)	
Total	03 (100)	05 (100)	05 (100)	10 (100)	09 (100)	07 (100)	

ICU: Intensive care unit

loss, expected surgical difficulties, and longer duration of surgery. The informed decision was taken after discussion with the patient and the surgeon.

- Hypertension was the commonest comorbidity in 14 patients followed by stroke in four patients. There were three patients with diabetes mellitus, ischemic heart diseases and Old Pulmonary Koch's each. Memtsoudis *et al.* found that in a large study of total arthroplasties from 2006 to 2010 in US, 16.9% patients had uncomplicated diabetes, 14.1% had chronic obstructive pulmonary disease (COPD), 3.7% had previous myocardial infarction, and 3.6% had rheumatic disease.[8] Wei *et al.* found in a retrospective study of 5759 patients, that common comorbidities were hypertension (59.84%), diabetes mellitus (13.63%), and COPD (5.70%).[10]
- The mean duration of the surgery in the study was 212.5 min. Habicher *et al.* found that in a study of 130 patients, the duration of surgery was 135 min (107–171 min) in the goal directed fluid therapy group and 125 min (99–159 min) in the control group.[15]
- The mean pre-operative hemoglobin was 11.43 g/dL and the mean post-operative hemoglobin was 9.05 g/dL. There was a difference of 2.38 g/dL. The mean blood loss in the study was 778.2 mL. Singh *et al.* found that the mean intraoperative blood loss was 489 mL (without tranexamic acid) and 339 mL (with tranexamic acid).[16] Peck *et al.* found that the estimated intraoperative blood loss was 845 mL (with tranexamic acid) and 1095 mL (without tranexamic acid) [Figure 3].[17]
- Singh *et al.*,[16] Peck *et al.*,[17] and Park *et al.*[18] found that the blood loss was lesser with tranexamic acid. It was found to be similar in our study, as seen in Table 4.
- Out of 26 males, 23 (88.46%) were anemic preoperatively and out of 13 females, 12 (92.31%) were anaemic preoperatively as per World Health Organization (WHO) classification for anaemia. Saleh *et al.* found that the prevalence of anaemia in elective major orthopedic surgeries is 20% and perioperative transfusions could be avoided.[19]
- The mean blood transfusion during the procedure was 163.4 mL. Twenty patients (51%) required blood transfusion during surgery. Only one patient (2.56%) was given fresh frozen plasma in the study. Saleh *et al.* found that 12 out of the 16 patients who underwent revision hip surgeries required blood transfusion.[19] Mahadevan *et al.* found that 73 patients (50%) out of 146 patients who underwent revision hip arthroplasties required blood transfusion.[19]
- The mean crystalloids given during the procedure was 1139.2 mL. Habicher *et al.* found that in a study of 130 patients, average of 725 mL crystalloids (500–100 mL) was given in the goal directed fluid therapy group and average 1500 mL was given in the control group.[15]
- The mean colloids given during the procedure was 252.5 ml. Twenty-three patients (58.97%) were given colloids in the study. Habicher *et al.* found that in a study of 130 patients, average of 1250 mL (1000–1750 mL) colloids was given in the goal directed fluid therapy group and average of 500 mL (500–1000 mL) was given in the control group.[15]

Table 7: General anaesthesia versus neuraxial anaesthesia

Outcome	General anaesthesia *n* (%)	Neuraxial anaesthesia *n* (%)
Number of patients	6 (15.38)	33 (84.61)
Duration of surgery	170 min	220.3 min
Blood loss	650 mL	801.51 mL
Blood transfusion	151.66 mL	165.63 mL
Inotropic needs	1 (16.66)	5 (15.15)
Postop ICU stay	0 (0)	2 (6.06)

ICU: Intensive care unit

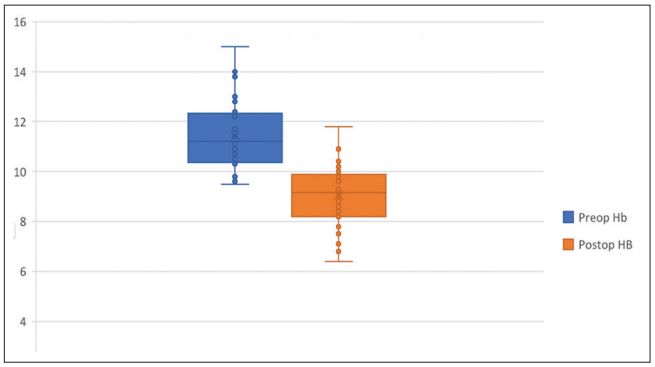

Figure 3: Comparison between pre-operative and post-operative haemoglobin

- 06 (15.38%) patients needed the requirement of inotropes during the surgery. The inotropes were started in view of major blood loss and non-maintenance of haemodynamics. Out of six patients, four were weaned off of inotropic supports in the immediate post-operative management. Habicher *et al.* found that in a study of 130 patients, 28 patients in the goal directed fluid therapy group and one patient in the control group required inotropes during the surgery.[15]
- Two patients (5.12%) were shifted to PACU for post-operative monitoring in view of major blood loss, non-maintenance of haemodynamics, and need for inotropic supports. Both of them were induced under CNB and had a drop of post-operative hemoglobin by around 3 g/dL.
- The limitations of this study include the single center study, lack of randomization and the lack of information about the type of implants and their influence on the perioperative outcome.[3,7]

CONCLUSION

The role of tranexamic acid in the improvement of perioperative outcome and reduction of the need for allogeneic blood transfusion is again confirmed by the study. The usage of neuraxial techniques over general anaesthesia is associated with almost similar perioperative outcomes. These findings suggest that the decision of anaesthetic technique should depend on the patient, surgical and anaesthetic risks of morbidity and mortality.

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Original Article

Assessment of the Relative Effectiveness of Negative Pressure Wound Therapy versus Standard Wound Dressing in Treatment of Pressure Ulcers

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Abstract

Introduction: A pressure ulcer (PU) is a localized injury to the skin and/or underlying tissue usually over a bony prominence. It occurs as a result of pressure or pressure in combination with shear and/or friction. In this study, the effect of negative pressure wound therapy (NPWT) on the outcome of PUs compared to Standard Wound Dressings (SWD) was observed.

Materials and Methods: The study was carried out in the Department of General Surgery and Department of Plastic Surgery, The Calcutta Medical Research Institute, Kolkata. A total of 58 consecutive patients having PU (of Stage 2, Stage 3, and Stage 4 according to the US National PU Advisory Panel Staging System, 2007) and fulfilling inclusion criteria were enrolled.

Results: The mean reduction in area of ulcer after treatment of the patients treated with SWD was significantly lower than that of the patients treated with NPWT ($P = 0.022$). The mean duration of treatment in days until granulation tissue appearance of the patients treated with NPWT was significantly lower than that of the patients treated with SWD ($P < 0.0001$). The cost of treatment was higher with NPWT than with SWD, but there was no significant difference in mean cost of the treatment of the patients ($P > 0.05$).

Conclusion: We conclude that NPWT is a better modality of treatment than SWD in healing of PUs. RCTs with a large sample size, longer duration of follow-up, and cost benefit analysis taking into account factors outside direct therapy costs need to be done to establish the superiority of NPWT over SWD.

Key words: Negative pressure wound therapy, Pressure ulcer, Standard Wound dressing

INTRODUCTION

A pressure ulcer (PU) is a localized injury to the skin and/or underlying tissue usually over a bony prominence. It occurs as a result of pressure or pressure in combination with shear and/or friction. Factors that contribute to the development of PUs are immobility, reduced sensation, shearing forces, moisture, friction, nutritional deficiency, and infection. PUs vary in severity and range from Stage I – non-blanchable erythema, Stage II – partial thickness loss of dermis, Stage III – full-thickness skin loss to Stage IV – full-thickness tissue loss with exposed bone, tendon or muscle, with Stages III and IV being severe.[1]

Surgery is an integral part of the treatment of PUs, but all patients are not fit for surgery. Apart from surgery, the treatment strategies for these wounds include the use of pressure-relieving devices, wound dressings, and, more recently, negative pressure wound therapy (NPWT).

Wound dressing with gauze has become the most widely used surgical dressing since Johnson and Johnson began mass-producing a sterile surgical dressing by sterilizing cotton yarn and thread in 1891.[2] Although wet-to-dry

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dressings have gained popularity throughout much of the 20th century, many investigations have published reports on the negative aspects of this method. Ovington states, "removal of a wet-to-moist dressing that has dried may then cause re-injury of the wound, resulting in pain and delayed wound healing." Gauze dressings have been reported to cause local tissue cooling during the evaporation period in wet-to-dry dressings. This cooling results in reflex vasoconstriction, hypoxia, impaired leukocyte, and phagocyte activity and increased affinity of hemoglobin for oxygen; all of which contribute to impaired wound healing. Removal of these dressings when dry can also lead to patient discomfort and pain.[3] The mechanical debridement during removal of these dressings can lead to cross-contamination of wounds by dispersion of bacteria into the air on removal. The non-selective mechanical debridement of healthy adjacent tissue is among another negative aspect of this wound care method8. Lawrence demonstrated that bacteria can pass through up to 64 layers of dry gauze in an *in vitro* study. It is permeable to exogenous bacteria and is associated with a higher infection rate than with transparent films or hydrocolloids.[4] While the materials are inexpensive, they do require frequent changes and the related nursing expense needs to be factored in when determining their true cost. Systematic reviews by Westby *et al.*[5] were unable to determine, in which dressings or topical agents are the most likely to heal PUs, and it is generally unclear whether the treatments examined are more effective than saline gauze. More research is needed to determine whether particular dressings or topical agents improve the probability of healing of PUs.

NPWT, which was developed at Wake Forest University (Winston-Salem, North Carolina) in the early 1990s, consists of an open-cell foam dressing covered with an adhesive drape. In spite of these claims, there is a growing recognition of a lack of high-quality research evidence to support the use of NPWT.[6] Several systematic reviews were unable to draw conclusions about the relative effectiveness of NPWT for the treatment of any wound including PUs, and they recommended that independent better quality research is needed.

This study aims to observe the effect of NPWT on the outcome of PUs compared to standard wound dressings (SWD). This will help us find whether NPWT is better than SWD and, therefore, provide the patients with better treatment options, to reduce their morbidity. This study will also provide information to PU patients about ulcer care and prevention of PUs. It will also provide an opportunity to train medical personnel to detect and treat adequately while helping to decrease economic and psychological trauma to the patient by improving the quality of life.

Aims and Objectives

Aim

The aim of this study was to assess the relative effectiveness of NPWT versus standard wound dressing in treatment of PUs.

Objectives

The objectives if this study were to assess and to compare the following between the two groups:

1. Reduction of surface area (length × breadth) of the wound.
2. Duration of treatment until granulation tissue appearance.
3. The cost of treatment (out of pocket expense for availing either approach).

MATERIALS AND METHODS

Study Site

The study was conducted at the Calcutta Medical Research Institute, Kolkata.

Study Population

The source of data for study was the patients of PU (of Stage 2, Stage 3, and Stage 4 according to the US National PU Advisory Panel Staging System, 2007), who were admitted during the period of 12 months commencing from June 2016 in the Departments of General surgery and Plastic Surgery at the Calcutta Medical Research Institute, Kolkata.

Inclusion Criteria

The following criteria were included in the study:

- Age between 18 and 85 years.
- Either sex.
- The patients having PU (Stage 2, Stage 3, and Stage 4 according to the US National PU Advisory Panel Staging System, 2007).

Exclusion Criteria

The following criteria were excluded from the study:

Patients with

- Grossly infected wounds
- Bleeding disorders
- Necrotic tissue in eschar
- Untreated osteomyelitis
- Actively bleeding wound.

Study Design

This study was prospective, observational, parallel-arm, and outcomes study. To avoid bias, each patient was alternatively allocated into two groups. Hence, the patients in two groups were in the ratio of 1:1.

RESULTS AND DISCUSSION

The present study is a prospective, observational study aimed to assess the relative effectiveness of NPWT versus standard wound dressing in the treatment of PUs. With reference to study done by Ashby *et al.*[7] with 99% power at 1% level of significance, in each group, 29 patients were included in the study.

The mean age (Mean ± SD) of patients in the NPWT group was 65.24 ± 8.37 years and in the Standard Wound Dressing group was 64.28 ± 8.13 years. Chi-square (χ^2) test showed that there was no significant association between age and patients of the two groups ($P = 0.98$). t-test showed that there was no significant difference between the mean age of the two groups ($P = 0.36$). Thus, the patients of the two groups were age matched, and hence, the patients of the two groups were comparable with reference to age.

In our study, Stage 3 PUs were more as compared to Stage 4 and Stage 2. The percentage of Stage 3 ulcer was higher in NPWT group, whereas the percentage of Stage 4 ulcer was higher in standard group; however, this distribution was statistically identical in the two groups with *P* value = 0.85. Thus, the stages of ulcers were more or less equally distributed among the two groups.

A majority of patients of this study were admitted for neurological disorder (21 out of 58) followed by trauma (15 out of 58), chronic renal diseases (eight out of 58), cardiovascular disorder (five out of 58), chronic respiratory illnesses (four out of 58), and for other reasons (five out of 58). There was no significant difference between comorbidity among patients of the two groups ($P = 0.42$), and hence, they were comparable in terms of comorbidity. Type II Diabetes Mellitus (T2DM) was found in 12 patients as comorbidity. There was no significant association between status of T2DM and patients of the two groups ($P = 0.99$). Thus, the patients of the two groups were comparable for presence or absence of T2DM.

Anemia was found in eight patients of NPWT group and in five patients of the Standard Wound Dressing group. Total 13 (22.41%) of patients had anemia. Statistically, the distributions of anemic patients in the two groups were similar with *P* value of 0.34. Furthermore, in the study out of 58 patients, 10 (17.2%) of the patients had low serum albumin. There was no significant difference in distribution of low serum albumin patients in the two groups ($P = 0.49$).

Wound culture revealed presence of microorganisms in 55 patients. Most common organism isolated was *E. Coli*, followed by *Pseudomonas*, *Staphylococcus*, *Klebsiella*, *Acinetobacter*, *Citrobacter,* and *Streptococcus*. No micro-organisms were isolated in three cases and all of which belonged to Stage 2 PUs. The association of micro-organisms in the two groups was found to be nearly identical ($P = 0.79$).

The mean area of ulcer before treatment (Mean ± SD) in patients of NPWT group was 74.68 ± 30.81 cm2 (range 15–132 cm^2), and in standard wound dressing group, it was found to be 73.51 ± 30.40 cm^2 (range 24–144 cm^2). t-test showed that there was no significant difference between the mean area of ulcer before treatment of the two groups ($P = 0.85$). Thus, the patients of the two groups were similar with respect to area of ulcer before treatment.

The mean area of ulcer (Mean ± SD) after treatment of patients with NPWT group was 36.58 ± 25.01 cm^2 (range 5–92 cm^2), and with standard wound dressing group, it was found to be 44.57 ± 23.37cm^2 (range 0–90 cm^2). t-test showed that the mean area of ulcer after treatment of the patients treated with Standard Wound Dressing was significantly higher than that of the patients treated with NPWT ($P = 0.011$) (Table 1).

The mean reduction in area of ulcer after treatment (Mean ± SD) of the patients with NPWT group was 37.58 ± 19.54 cm^2 (range 5–80 cm^2) and with standard wound dressing group was 28.95 ± 17.96 cm^2 (range 4–78 cm^2). t-test showed that the mean reduction in area of ulcer after treatment of the patients treated with Standard Wound Dressing was significantly lower than that of the patients treated with NPWT ($P = 0.022$) (Table 2).

The mean number of surgical debridement (Mean ± SD) of the patients with NPWT group was 2.24 ± 1.43, and with standard wound dressing group, it was 4.28 ± 2.22. t-test showed that the mean number of surgical debridement of the patients treated with NPWT was significantly lower than that of the patients treated with Standard Wound Dressing ($P < 0.0001$) (Table 3).

The mean duration of treatment until granulation tissue appearance (Mean ± SD) of patients with NPWT was 21.45 ± 5.81 days (range 10–32 days) and with standard wound dressing group, it was 36.24 ± 14.16 days (range 8–53 days). t-test showed that the mean duration of treatment in days until granulation tissue appearance of the patients treated with NPWT was significantly lower than that of the patients treated with Standard Wound Dressing ($P < 0.0001$) (Table 4).

The mean number of dressing change (Mean ± SD) of patients with NPWT group was 5.34 ± 1.37 (range 3 – 8) and with standard wound dressing group, it was 36.24 ± 14.16 (range 8–53). t-test showed that the mean number of dressing change of the patients treated with NPWT was

significantly lower than that of the patients treated with Standard Wound Dressing ($P < 0.0001$) (Table 5).

The mean cost of the treatment (Mean ± S.D) of the patients treated with NPWT group was INR 32,836.21 ± 10,874.75 and that of the patients treated with Standard Wound Dressing was INR 32,682.59 ± 16,529.11. t-test showed that there was no significant difference in mean cost of the treatment of the patients treated with NPWT and that of the patients treated with Standard Wound Dressing ($P > 0.05$). The cost of treatment was higher with NPWT than with standard wound dressing (Table 6).

The area of ulcer after treatment was significantly decreased ($P = 0.011$) in NPWT group as compared with Standard Wound Dressing which was in concordance with study conducted by Dwivedi *et al.*,[8] where length and width of ulcer decreased significantly ($P < 0.01$) in NPWT group.

The mean reduction in area of ulcer after treatment of the patients treated with Standard Wound Dressing was significantly lower than that of the patients treated with NPWT ($P = 0.022$). Similar findings were observed in studies done by Srivastava *et al.*,[9] Moues *et al.*,[10] and Dwivedi *et al.*[8] comparing NPWT with Standard Wound Dressing by moist gauze (*P* value=0.0001, <0.05 and <0.01, respectively). In study conducted by Ford *et al.*,[11] it was found that the mean percent reduction in ulcer volume was 42.1% with gel products compared to 51.8% with VAC ($P = 0.46$). Isago *et al.*,[12] in their study, observed that following NPWT treatment, wound area reduced by an average of 55%. Our study result is equivocal with that of above two studies[11,12] with respect to percent reduction, as there is 40% reduction in area with standard wound dressing and 51% with NPWT considering the mean area of ulcer before initiation of treatment were 74.68 ± 30.81 cm^2 and 73.51 ± 30.40 cm^2 and following treatment was 36.58 ± 25.01 cm^2 and 44.57 ± 23.37 cm^2, respectively, for NPWT and standard wound dressing.

The mean duration of treatment (in days) until the appearance of healthy granulation tissue in patients treated with NPWT was significantly lower than that of the patients treated by Standard Wound Dressing ($P < 0.0001$) which was in agreement with study conducted by De Laat *et al.*[13] ($P < 0.001$). In another study conducted by Dwivedi *et al.*,[8] they found that conversion of slough into red granulation tissue was significantly higher in NPWT group ($P = 0.001$). In the present study, appearance of healthy granulation tissue was faster in NPWT group, and hence, closure of wound was earlier in NPWT group than standard wound dressing group; an observation which is in agreement with the study of Mody *et al.*,[14] who conducted a randomized controlled trial comparing a locally constructed TNP device with wet-to-dry gauze dressings on varied wound etiologies, including diabetic foot ulcers, PUs, cellulitis/fasciitis, and other types of ulcers. In PU sub-set, the authors found statistically significant differences ($P = 0.05$) in the time of closure of wound between the two treatment groups, TNP group closing earlier than gauze dressing group. Moues *et al.*,[10] in their study, found a tendency toward a shorter duration of therapy with NPWT, which was most prominent in

Table 1: Distribution of area of ulcer after treatment of the patients of the two groups

Area of ulcer (cm^2)	NPWT	Standard wound dressing	Total
0–5	0	0	0
Row %	0.0	0.0	0.0
Col %	0.0	0.0	0.0
6–29	14	7	21
Row %	66.7	33.3	100.0
Col %	48.3	24.1	36.2
30–54	8	10	18
Row %	44.4	55.6	100.0
Col %	27.6	34.5	31.0
55–79	5	9	14
Row %	35.7	64.3	100.0
Col %	17.2	31.0	24.1
80–92	2	3	5
Row %	40.0	60.0	100.0
Col %	6.9	10.3	8.6
Total	29	29	58
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±SD	36.58±25.01	44.57±23.37	
Median	31.68	36.00	
Range	5–92	12–90	

Table 2: Distribution of reduction in area of ulcer after treatment of the patients of the two groups

Reduction in Area of ulcer (cm^2)	NPWT	Standard wound dressing	Total
4.0–9.9	2	2	4
Row %	50.0	50.0	100.0
Col %	6.9	6.9	6.9
10.0–29.9	9	15	24
Row %	37.5	62.5	100.0
Col %	31.0	51.7	41.4
30.0–49.9	10	7	17
Row %	58.8	41.2	100.0
Col %	34.5	24.1	29.3
50.0–79.9	6	5	11
Row %	54.5	45.5	100.0
Col %	20.7	17.2	19.0
80.0–100.0	2	0	2
Row %	100.0	0.0	100.0
Col %	6.9	0.0	3.4
Total	29	29	58
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±SD	37.58±19.54	28.95±17.96	
Median	34.00	24.00	
Range	5–80	4–78	

Table 3: Distribution of number of debridement of the patients of the two groups

Number of debridement	NPWT	Standard Wound Dressing	Total
0–2	18	6	24
Row %	75.0	25.0	100.0
Col %	62.1	20.7	41.4
3–4	9	10	19
Row %	47.4	52.6	100.0
Col %	31.0	34.5	32.8
5–6	2	8	10
Row %	20.0	80.0	100.0
Col %	6.9	27.6	17.2
7–8	0	5	5
Row %	0.0	100.0	100.0
Col %	0.0	17.2	8.6
Total	29	29	58
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±SD	2.24±1.43	4.28±2.22	
Median	2	4	
Range	0–5	1–8	

Table 4: Distribution of duration of treatment till granulation tissue appearance of the patients of the two groups

Duration of treatment till granulation tissue appearance (in days)	NPWT	Standard Wound Dressing	Total
<10	0	1	1
Row %	0.0	100.0	100.0
Col %	0.0	3.4	1.7
10–14	3	3	6
Row %	50.0	50.0	100.0
Col %	10.3	10.3	10.3
15–21	13	0	13
Row %	100.0	0.0	100.0
Col %	44.8	0.0	22.4
22–28	10	2	12
Row %	83.3	16.7	100.0
Col %	34.5	6.9	20.7
29–35	3	9	12
Row %	25.0	75.0	100.0
Col %	10.3	31.0	20.7
>35	0	14	14
Row %	0.0	100.0	100.0
Col %	0.0	48.3	24.1
Total	29	29	58
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±SD	21.45±5.81	36.24±14.16	
Median	20	35.00	
Range	10–32	8–53	

Table 5: Distribution of number of dressing change of the patients of the two groups

Number of dressing change	NPWT	Standard Wound Dressing	Total
<10	29	1	30
Row %	96.7	3.3	100.0
Col %	100.0	3.4	51.7
10–29	0	7	7
Row %	0.0	100.0	100.0
Col %	0.0	24.1	12.1
30–49	0	14	14
Row %	0.0	100.0	100.0
Col %	0.0	48.3	24.1
50–59	0	7	7
Row %	0.0	100.0	100.0
Col %	0.0	24.1	12.1
TOTAL	29	29	58
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±SD	5.34±1.37	36.24±14.16	
Median	5	35.00	
Range	3 – 8	8 – 53	

Table 6: Distribution of cost of the treatment of the patients of the two groups

Cost of the treatment (in Rs.)	NPWT	Standard wound dressing	Total
5000–10000	0	4	4
Row %	0.0	100.0	100.0
Col %	0.0	13.8	6.9
10001–20000	4	4	8
Row %	50.0	50.0	100.0
Col %	13.8	13.8	13.8
20001–30000	10	8	18
Row %	55.6	44.4	100.0
Col %	34.5	27.6	31.0
30001–40000	8	1	9
Row %	88.9	11.1	100.0
Col %	27.6	3.4	15.5
40001–56000	7	12	19
Row %	36.8	63.2	100.0
Col %	24.1	41.4	32.8
Total	29	29	58
Row %	50.0	50.0	100.0
Col %	100.0	100.0	100.0
Mean±SD	32,836.21 ± 10,874.75	32,682.59 ± 16,529.11	
Median	34500.00	28500.00	
Range	15,000–54,000	8,554–55,168	

late-treated wounds, but the difference was statistically not significant ($P = 0.19$). Our study was also similar to studies like Isago *et al.*[12] and Ashby *et al.*,[7] in which it was found that duration of therapy was less with NPWT compared with standard wound dressing. In the present study, the mean duration of treatment until granulation tissue appearance of patients with NPWT was 21.45 ± 5.81 days which was in concordance with study conducted by Gupta *et al.*,[15] where robust granulation tissue formation was found after 3–4 weeks of treatment with NPWT. In a case report by Batra *et al.*,[16] VAC was applied every 5th day until near-complete healing was achieved, and it took six cycles, a finding which was in agreement with our study. Wanner *et al.*[17] compared NPWT with a traditional wound dressing with gauze soaked in Ringer's solution. They found that the decrease in wound volume was similar in the two groups

and the two methods were found equally effective in the formation of granulation tissue.

Even though the cost of treatment was higher in NPWT group, but the difference in the mean cost of the treatment of the patients treated with NPWT group (INR 32,836.21 ± 10,874.75) and that of the patients treated with Standard Wound Dressing (INR 32,682.59 ± 16,529.11) was statistically insignificant ($P > 0.05$). Higher cost of treatment in NPWT group was also observed in studies done by Moues *et al*.[10] and Gupta *et al*.[15] Moues *et al*.,[10] in their study, found that vacuum therapy had higher material costs and the mean material expenses for wounds treated with vacuum therapy compared with conventional therapy was significantly higher ($P < 0.0001$), but on contrary, there was significantly lower mean nursing expenses for vacuum therapy than conventional therapy ($P < 0.0001$). Hospital stay costs were lower in the vacuum therapy group than in the conventional treatment group ($P < 0.043$). Overall, there was no significant difference in total costs per patient between the two therapies with conventional therapy being equally as expensive as NPWT. In our study, we considered the direct therapy costs (cost of consumables) which were higher for NPWT patients, but on contrary the cost of surgical debridement, nursing expenses and hospitalization costs were lower in NPWT group. However, studies such as Srivastava *et al*.,[9] Dwivedi *et al*.,[8] and Mody *et al*.[14] found that direct therapy costs are lower with NPWT but not significant. In these studies,[8,9,14] the investigators used locally constructed low cost NPD or TNP devices, whereas in our study, standard NPWT machine of Datt Mediproducts Pvt. Ltd. and VEL NeXT dressing materials for NPWT group were used.

We observed that the mean number of dressing change of the patients treated with NPWT was significantly lower than that of the patients treated with Standard Wound Dressing ($P < 0.0001$), a finding which is in agreement with various other similar studies.[10,13] It was also found that the mean number of debridement of the patients treated with NPWT was significantly lower than that of the patients treated with Standard Wound Dressing ($P < 0.0001$) which has not been analyzed in other studies.

CONCLUSION

In our study, we have found that NPWT brings more reduction in ulcer area, early appearance of granulation tissue, lesser need of surgical debridement, and lesser need of change of dressing compared to standard wound dressing in all stages of PUs. All these parameters are statistically significant and are in favor with NPWT. In our study, we observed that effectiveness of NPWT is more in higher stages of PU such as Stage 3 and Stage 4.

We did not find any complication in all cases of NPWT. We also did not find any technical difficulty with NPWT. Thus, NPWT is easy to apply and safe method of wound therapy.

Regarding cost of treatment, we found that it is on higher side with NPWT but not significant. In our study, we have taken the direct therapy costs. Future studies should focus on factors outside direct therapy costs also such as hospitalization costs, nursing personnel costs, and costs for surgical procedures.

We conclude that NPWT is a better modality of treatment than standard wound dressing in healing of PU. RCTs with a large sample size, longer duration of follow-up, and cost benefit analysis taking into account factors outside direct therapy costs need to be done to establish the superiority of NPWT over standard wound dressing.

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Original Article

Laproscopic Findings in Patients with Normal Hysterosalpingography (HSG) Findings and Unexplained Infertility

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Abstract

Introduction: Infertility is a disease of male or female reproductive system defined by the failure to achieve pregnancy within 12 months or more of regular unprotected sexual intercourse. The frequency varies from 5% to 15% in different communities that are approximately one in ten couples (about 80–90 million of the world population). It has been estimated that the diagnostic laparoscopy helps in finding the infertility factor in 21–68% cases of unexplained infertility as seen in different studies.

Materials and Methods: The present study was conducted in the Department of Obstetrics and Gynecology of Lalla Ded Hospital, GMC Srinagar, J and K, a tertiary care center, for 24 months from June 2018 to June 2020. A total of 64 cases of primary and secondary infertility were studied to know the role of diagnostic laparoscopy in the evaluation of infertility. The percentage of patients with primary infertility was higher (71.88%) as compared to patients with secondary infertility (28.12%).

Results: The results of the present study showed that the mean duration of primary infertility and mean age was 4.424 years and 30.23 years, respectively, while as in cases of patients with secondary infertility, the mean duration of infertility and mean age was calculated as 5.722 years and 32.889 years, respectively. In the present study on 64 patients, the normal laparoscopic findings were seen in 22 patients (34%) and abnormal findings were discovered in 44 patients (66%). The most frequent laparoscopic finding in present study was endometriosis seen in 22 (34%) patients, the frequency of pelvic adhesions was 14.1% with more number of patients with secondary infertility. Tubal factors (tubal blockade and hydrosalpinx) were less prevalent causes of infertility in the present study constituting 7.8% and 4.7%, uterine myomas were seen in 4.7%, and all in cases of primary infertility. Therapeutic intervention (adhesionolysis, drilling of cysts, and myomectomy) was done in 22% of patients.

Conclusion: From the present study, we concluded that diagnostic laparoscopy is the gold standard tool in the evaluation of female infertility.

Key words: HSG, IVF, IU

INTRODUCTION

Infertility is a disease of male or female reproductive system defined by the failure to achieve pregnancy within 12 months or more of regular unprotected sexual intercourse. However, it holds true for a female with age <35 years.[1] In women more than 35 years of age, infertility workup should begin after 6 months only. It may be primary or secondary. The primary infertility refers to couple who have never conceived. Secondary infertility indicates previous pregnancy irrespective of the outcome (abortion or live birth) but failure to conceive subsequently.[2] Infertility is a global problem. The frequency varies from 5% to 15% in different communities that are approximately one in ten couples (about 80–90 million of the world population). In India, the frequency of infertility is also more than 10% with a whooping 20 million population as infertile.[3]

The causes of infertility with relative prevalence are as following:[4]

- Male factor – 17–28%
- Both male and female factors – 8–39%
- Female factor – 33–40%

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- Unexplained – 8–28%

Approximately 10–30% of couples are diagnosed with unexplained infertility, in which basic infertility ovulation reveals normal semen parameters, evidence of ovulation, patent fallopian tubes, and no other cause of infertility.[5] Patients with unexplained infertility may feel.

Reassured that even after 12 months of attempting, 20% will conceive in the following 12 months and 50% in following 36 months.[6] It is the diagnosis of exclusion. The variability in incidence is dependent on depth of investigation protocol extended to the couple. In Kashmir, the incidence is estimated to be 15% approximately.[7] Proposed mechanisms for unexplained infertility are as follows:

1. Luteinized unruptured follicle syndrome: It is thought to occur in 25% of patients with unexplained infertility. The condition involves luteinizing of follicle that has failed to rupture and releases its oocyte, leading to a normal menstrual cycle.[8]
2. Immunological factors: Anti-sperm antibodies and imbalance in T lymphocyte population.[9]
3. Infection: *Chlamydia tracohomatis*, *Ureaplasma urealyticum*, and *Mycoplasma genitlium*.[10]
4. Undiagnosed pelvic pathology: Peri-tubal adhesions and endometriosis.[11]
5. Occult male or oocyte factors: Impaired sperm DNA integrity and premature zona hardening (oocyte factor).[12]

In the present era, laparoscopy is the main tool in the armamentarium of infertility workup, which serves as both diagnostic and therapeutic modality. In cases of unexplained infertility after evaluation of both the partners, it helps to recognize endometriosis, pelvic adhesions, hydrosalpinx, and other peritoneal factors. It is particularly cost effective in the young couples as compared to fertility therapy. It has been estimated that the diagnostic laparoscopy helps in finding the infertility factor in 21–68% cases of unexplained infertility as seen in different studies. The benefit of laparoscopy is that some therapeutic procedures for infertility can be done at the same setting such as adhesionolysis, drilling of polycystic ovaries, and tubal nich surgeries. Laparoscopy also helps in devising the future management depending on the cause like whether to go for IUI or IVF.

Aims and Objectives

The study was accomplished to attain the subsequent objectives:

1. To investigate the role of Laparoscopy as diagnostic tool in unexplained infertility and normal Hysterosalpingography findings.
2. To study different pelvic causes of unexplained infertility.
3. To bring out possible interventions where ever required.

MATERIALS AND METHODS

The present study was conducted in the Department of Obstetrics and Gynecology of Lalla Ded Hospital, GMC Srinagar, J and K, a tertiary care center, for 24 months from June 2018 to June 2020. A total of 64 cases of primary and secondary infertility were studied. After taking detailed history, clinical examination, investigations, and proper written consent, patients were taken up for diagnostic laparoscopy post menstrually in proliferative phase of the menstrual cycle.

Inclusion Criteria

The following criteria were included in the study:

- Patients with unexplained infertility in reproductive age group.
- Patients with history of primary as well as secondary infertility.
- Patients having normal hysterosalpingography findings.

Exclusion Criteria

The following criteria were excluded from the study:

- Patients with documented anomalies of reproductive tract on HSG (Hysterosalpingography).
- Patients having any contraindication to laparoscopic procedures such as previous major surgeries, peritonitis, hernia, or large pelvic mass.
- Patients having contraindication to general anesthesia.
- Major male infertility.

Procedure

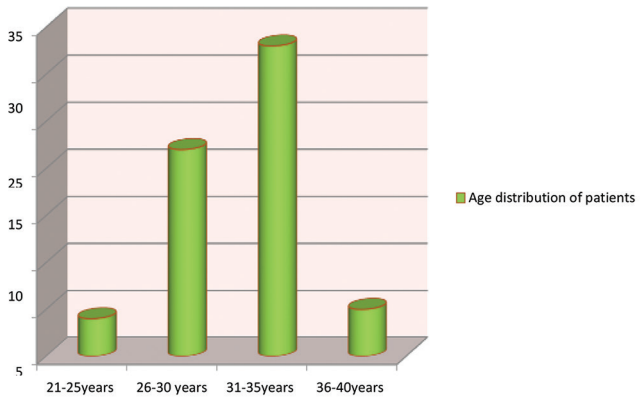
After clinical examination, diagnostic laparoscopy was performed to identify any possible pelvic pathology. A small incision in infra-umbilical region was made. Veres needle introduced and pneumoperitoneum created with 2–3 L of CO_2 at the rate of 1 L per minute. Then, trocar and cannula were inserted, after elevating the abdominal wall. Laparoscope was inserted, after removing the trocar. Then, the fibro-optic light cable was connected to the laparoscope and the light source. The camera was also connected to the laparoscope. The uterine manipulator was used to elevate the uterus especially in retroverted uterus and to mobilize the adnexa.

The systematic view of the pelvis was undertaken, commencing from the uterus. The fundus, anterior surface, and posterior surface of uterus was assessed. The fluid in pouch of douglas and any evidence of scarringa and endometriosis was identified. Each uterosacral ligament was looked for endometriosis scarring and each adnexa was thoroughly visualized. The anterior surface of both ovaries and fallopian tubes was inspected. The inferior surface of the ovary and

posterior leaf of the broad ligament up to uterosacral ligament were evaluated. The fallopian tubes were examined from its distal to proximal segment, and any evidence of distal tubal occlusion (hydrosalpinx) fimbrial phimosis was assessed.

RESULTS

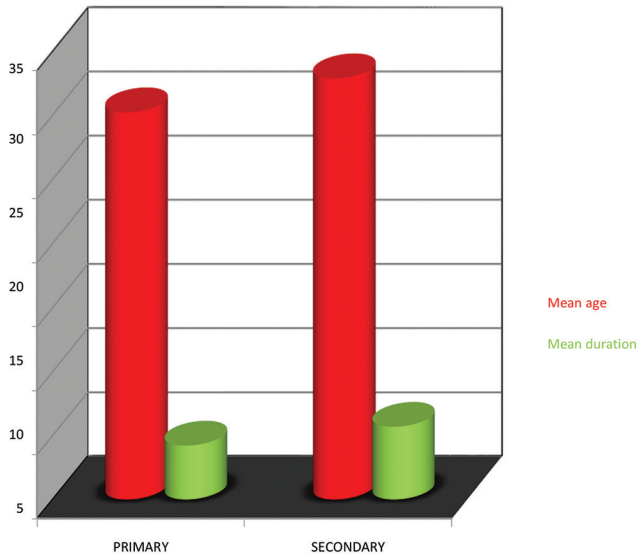
- Out of total 64 patients, the percentage of patients with the primary infertility was 71.88%, while as the percentage of patients with secondary infertility was 28.12%.
- Approximately half (51.5%) of the patients were in the age group of 31–35 years.

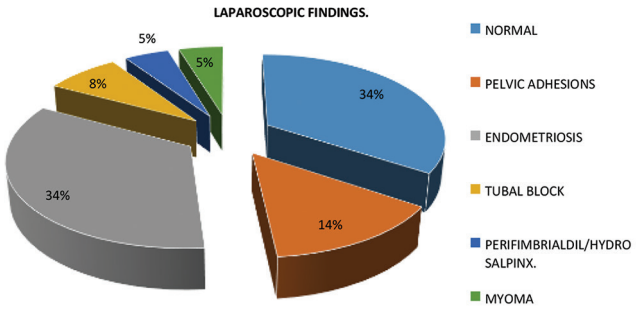


Duration of infertility (in years)			
S. NO	**Duration (Years)**	**No.**	**% Age**
1.	<or=03	16	25
2.	04–06	42	65.6
3.	>06	06	9.3

- The duration of infertility in 16 patients (25% of total patients) was approximately of 3 years, while in 42 patients (65.6), the duration of infertility under evaluation was of 4–6 years, and in 6 (9.3 %) patients, it was of more than 6 years.
- The mean duration of the primary infertility (total 46 patients) and mean age was 4.4 years and 30.2 years respectively, while as in cases of patients with secondary infertility, the mean duration of infertility and mean age was calculated as 5.7 years and 32.8 years, respectively. The mean age in primary and secondary infertility had statistically significant relationship with each other, while as the durations of infertility between two has no statistical significance.

Out of 64 patients, the laparoscopic finding in 22 (34.4%) patients was normal, 09 (14.1%) patients showed pelvic adhesions, 05 (7.8%) patients had tubal block on laparoscopy, perifimbrial dilatation/hydrosalpinx and uterine myoma was seen in 03 (4.7%) patients each, and 22 (34.4%) patients had endometriosis as laparoscopic findings.





Ta ble 1: Showing frequency of laparoscopic findings

S. No.	Laparoscopic findings	Frequency	Percentage	Cumulative Percentage
01.	Normal	22	34.4	34.4
02.	Pelvicadhesions	09	14.1	48.5
03.	Endometriosis	22	34.4	82.9
04.	Tubalblock	05	7.8	90.7
05.	Perifimbrial Dilatation/ Hydrosalpinx	03	4.7	95.4
06.	Uterine Myoma	03	4.7	100

Table 2: Showing relation of laparoscopic findings with infertility type

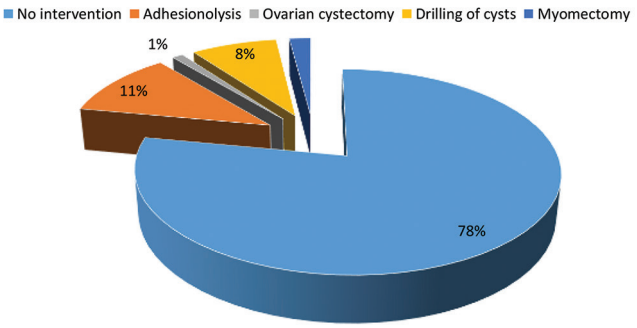
S. No	Lap. Finding	Infertility type Primary	Infertility type Secondary	Total
1.	Normal	12	10	22
2.	Pelvic Adhesions	06	03	09
3.	Endometriosis	18	4	22
4.	Tubal Block	04	01	05
5.	Myoma Uterus	03	00	03
6.	Perifimbrial Dilatation/ Hydrosalpinx	03	00	03
	Total	46	18	64

- The primary infertility was seen in 46 patients, out of which 12 patients had normal laparoscopic findings, six patients had pelvic adhesions, and 18 patients were with endometriosis in different stages (seven in Stage I, six in Stage II, three patients in Stage III, and Stage IV endometriosis was seen in two patients). When the patients with normal laparoscopic findings were compared with patients with abnormal laparoscopic findings, the relationship was statistically significant; however, in cases of secondary infertility, 18 in number, the normal laparoscopic findings were seen in ten patients and abnormal findings were seen in eight patients.

Laparoscopic interventions were done in the same setting as follows

S. no	Intervention	No. of patients	Percentage
1.	No intervention	50	78.1
2.	Adhesionolysis	07	10.9
3.	Ovarian cystectomy	01	1.5
4.	Drilling of cysts	05	7.8
5.	Myomectomy	01	1.5
	Total	64	100

- Among 64 patients, 50 (78.1%) patients had no intervention, while as 7 (10.9%) patients underwent adhesionolysis, one patient (1.5%) had ovarian cystectomy and one (1.5%) patients had undergone myomectomy, and five (7.8%) patients underwent drilling of cysts in the same sitting of laparoscopy [Tables 1 and 2].



DISCUSSION

In our prospective study conducted for 2 years in 64 patients with unexplained infertility, the percentage of patients with primary infertility was higher (71.88%) as compared to patients with secondary infertility (28.12%). Our results were similar to the study conducted by Bansal *et al.*[13] which revealed 64% cases of primary infertility and 36% cases of secondary infertility. The results of the present study showed that the mean duration of primary infertility (total 46 patients) and mean age was 4.424 years and 30.23 years, respectively, while as in cases of patients with secondary infertility, the mean duration of infertility and mean age was calculated as 5.722 years and 32.889 years, respectively. Our results were concordant to study conducted by Agarwal *et al.*,[13] where the mean age at presentation was 28 years in the primary infertility and 32 years in the secondary infertility. The duration of infertility was 2–5 years in majority of patients (59.1%) of the primary infertility, while it was over 5 years in majority of patients (77.7%) with the secondary infertility. None had <2 years of duration in case of primary or secondary infertility. Similar results were reported in a study by Ashraf and Metal.[14] In the present study on 64 patients, the normal laparoscopic findings were seen in 22 patients (34 %) and abnormal findings were discovered in 44 patients (66%). These results were similar to the study done by Bansal *et al.*,[13] where in their study, the percentage of normal findings on laparoscopy was 25% in the primary infertility cases, while as 75% patients were diagnosed with abnormal findings on laparoscopy. The laparoscopic findings in the present study were also concordant to Tsuji *et al.*,[15] Mushtaq *et al.,*[16] and Kumar *et al.*[17] Laparoscopic findings were normal in 19.3% of cases and abnormal in 80.3% of cases in Tsuji *et al.*[15] study, and similarly, 17.5% were normal and 82.5% were abnormal in Mushtaq R *et al.*[16] study and 18% were normal and 82% were abnormal in the study by Kumar *et al.*[17] The most frequent laparoscopic findings in the present study were endometriosis seen in 22 (34%) patients. Our result was concordant with the study conducted by Duraker *et al.*[18] which showed endometriosis as cause of infertility in 28.4% and 32% patients, respectively. Periovarian adhesions are factors responsible for inhibition of ovum pickup and transport. In the present study, the frequency of pelvic adhesions was 14.1% with more number of patients with secondary infertility. These results are comparable to study by Bansal *et al.*[13] and Setarabintekasem *et al.*,[19] who in their studies documented the percentage of adhesions as 14%and 19.1%, respectively.

Even though HSG is widely used for assessment of tubal patency, an accurate assessment of tubal status cannot be obtained by HSG alone. The correct assessment of tubal status can only be made through laparoscopy, which allows for direct visualization. Tubal factor (tubal blockade and hydrosalpinx) was less prevalent causes of infertility in the present study constituting 7.8% and 4.7%, respectively. The studies conducted by Shetty and Shetty,[20] Samal *et al.,*[21] and Agarwal and Anand[22] study showed tubal factor as the most common factor of primary infertility due to subclinical PIDs in young women and adolescents because of poor perineal hygiene, particularly during menstrual periods. However, in the present study, the tubal blockage including the cases involving perifimbrial hydrosalpinx was less prevalent, and more so in secondary infertility. In the present study, various laparoscopic procedures were done at the same sitting. Fifty (78.1%) patients had no intervention, while as 7 (10.9%) patients under went adhesionolysis, one patient (1.5%) had ovarian cystectomy,

1 (1.5%) patient had undergone myomectomy, and 5 (7.8 %) patients had undergone drilling of cysts. The laparoscopic procedures are cause driven, and hence, any findings on laparoscopy can change line of management for infertility. Thus, the laparoscopy is a best modality for diagnostic as well as therapeutic intervention and when these laparoscopic procedures are compared with the data of many studies in terms of positive outcome of conception, these seem to be the modality of choice for any organic cause of infertility.

CONCLUSION

Following conclusions were drawn from the present study;

1. Primary infertility was the most common reason for diagnostic laparoscopic evaluation as 71.88% cases presented with the primary infertility. The secondary infertility was present in 28.12% cases.
2. Majority of the primary infertility group (51%) belonged to age group of 26–30 years and 48.1% of the secondary infertility cases presented in 31–35 years of age.
3. Majority of the primary infertility patients presented with 2–4 years duration and majority of the secondary infertility cases with more than 5 years duration of infertility.
4. Approximately 34% of cases had normal findings in diagnostic laparoscopy, whereas 66% of cases presented with pathological findings.
5. Most common pathological finding in the present study was endometriosis followed by pelvic adhesions.
6. Least common finding in present study was uterine myoma.
7. Therapeutic intervention (adhesiolysis, drilling of cysts and myomectomy) was done in 22% of patients.

Based on our results, we conclude that laparoscopy is beneficial for patients with unexplained infertility and normal HSG findings, because it is a reliable procedure in detecting specific causes of infertility in the pelvic cavity which is not diagnosed by other investigations. It provides direct and magnified view of all pelvic organs. It is a "definitive day care procedure" in evaluation of infertility, because it has the benefit of shorter hospital stay, less post-operative pain, and quick return of routine activity. Diagnostic laparoscopy can be used as a "ONETIME APPROACH" as evaluation and therapeutic procedures can be done in the same sitting as needed. From the present study, we can conclude that diagnostic laparoscopy is the gold standard tool in the evaluation of female infertility.

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Original Article

Peers' Perception Regarding Golden Proportion/ Golden Ratio: A Questionnaire Based Survey

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Abstract

Introduction: The previous studies evaluated the perception of laypersons to symmetric alteration of anterior dental aesthetics. However, no studies have evaluated the knowledge regarding the golden perception. These questionnaires determine the knowledge regarding the golden perception is observed by dental professionals.

Materials and Methods: A questionnaire-based survey was formulated and circulated in peer groups of dentistry. Profile photographs were intentionally altered with a software-imaging program and basic and advanced questionnaires were formed. Statistical analysis of the responses resulted in the establishment of threshold levels of perception for each group.

Results: There are certain areas in which statistically significant difference is found between orthodontist and others regarding perception of Golden proportion in their respective fields.

Conclusions: Basic knowledge regarding golden proportion is the need of the hour to change the perception of dental professionals and result in a more educated and informed approach in the treatment of each patient.

Key words: Aesthetics, Golden proportion, Peers perception

INTRODUCTION

Since time immemorial, nature has developed various patterns and processes with interesting characteristics. They have been used as an inspiration for a significant number of innovative models that can be extended to solve complex engineering and mathematical problems. One such exceptional pattern is Golden Ratio: An irrational number that appears frequently as an esthetic standard in art, architecture, and nature. Its distinctive mathematical properties lead to some interesting applications in many branches of science including human anatomy. The Golden proportion is considered as the most pleasing composition to human vision; however, it is not limited to esthetic beauty but its existence can also be in natural world through the body proportions of living beings, the growth patterns of many plants, insects, and also in the model of enigmatic universe. The properties of Golden section can be instituted and integrated in the pattern of mathematical series and geometrical patterns.[1]

Analysis of attractiveness of faces has long been a topic of research. The literature has identified many different factors that can be related to attractiveness. Here, in this study, we will analyze perception about the role of symmetry and Golden ratio in the determination of attractiveness of a face by focusing on the geometry of a face using actual faces. We found there are some differences in the criteria used by males and females to determine attractiveness.[2]

The purpose of this study was to determine whether asymmetric and symmetric anterior dental discrepancies and extraoral profile discrepancies are detectable by various groups of evaluators, and the extent of their knowledge and comprehension on concept of Golden ratio.

These data are invaluable in designing complex, interdisciplinary treatment plans, and to evaluate each scenario at dental professional level, possessing a comprehensive understanding of Golden ratio.

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MATERIALS AND METHODS

Different groups of raters were used in this study. For the same, questionnaire was made in the pattern of Google form and circulated to various groups of dental fraternity to evaluate and acquire their perception concerning "Golden section." All dentists were registered members under Dentist Act, 1948 in Dental council of India, including various region of India. They were selected randomly and Google form was sent to 150 individuals who were actively involved in members' association at different level. An ethical committee approval and patient consent are not applicable for questionnaire-based survey.

Variables

The different groups rated extraoral profile photographs and intraoral photographs on the account of need of correction of profile and teeth, respectively (from no need to severely needed); additionally sharing their number of years of experience and expertise in various fields of dentistry. The extraoral profile photograph of subject was intentionally altered using Dolphin Imaging Software 2D (version 11.8) to create various skeletal discrepancy [Figure 1]. Lateral cephalogram X-ray was digitized and its tracing overview was superimposed on extraoral profile photograph. These alterations were chosen based on their frequency and clinical significance to the face. The intraoral photographs include different degree of crowding and irregularities present in both dental arches which can be easily comprehended through intraoral frontal photographs [Figure 2].

The others questions were in form of thorough knowledge of Golden ratio.

Questionnaire

1. Years of Experience:
   - <5 years
   - 5–10 Years
   - More than 10 Years.
2. Area of Expertise:
   - Orthodontics
   - Prosthodontics
   - General dentist
   - Oral and Maxillofacial Surgeon
   - Any Other Please Specify.

Basic (B1) Category

3. Rate extraoral photographs based upon need of correction in facial profile (no Need to severely needed) Figure 1.
   - A,B,C,D,E
   - D,C,A,B,E
   - E,A,C,B,D
   - C,B,D,A,E
4. Rate intraoral front photograph based on need for correction of teeth (no need to severely needed) Figure 2.
   - B,C,A,D
   - C,B,A,D
   - A,C,D,B
   - A,B,C,D
5. The Golden ratio is claimed to appear in many fields, such as cosmology, theology, arts, architecture, botany, and others.
   - True
   - False
   - Do not Know.
6. The American mathematician, Mark Barr, has chosen Phi as the symbol for the Golden ratio. Phi is named after which of the following Greek sculptors?
   - Philips
   - Phidias
   - Phiviles
   - Phixels.
7. At present, the Golden ratio is symbolized by the Greek letter phi. Sometimes, it is also represented by another Greek letter. Which letter is it?

Figure 1: (a-e) Rate Extra oral photographs based upon need of correction in facial profile (no Need to severely needed)

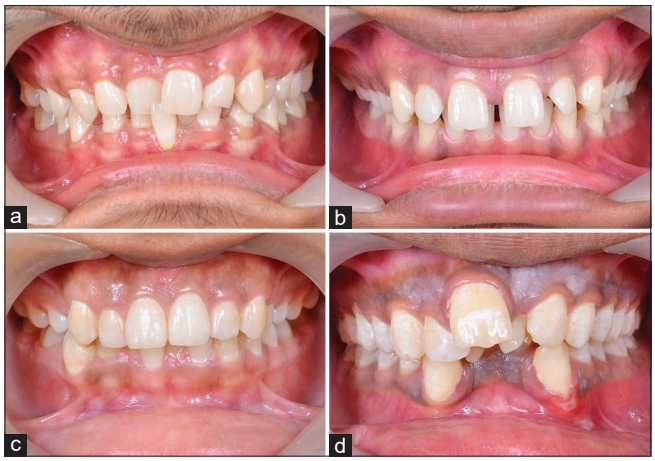

Figure 2: (a-d) Rate Intra oral front photograph based upon need for correction of teeth (no need to severely needed)

- Sigma
- Delta
- Tau
- Lambda.

8. In what way is the Golden ratio, phi, related to the Fibonacci sequence?
   - The ratio of two adjacent numbers in the Fibonacci sequence is exactly phi
   - There is no similarity
   - They were discovered by the same person
   - The ratio of two adjacent numbers in the Fibonacci sequence is approximately phi.

9. Do you think does Golden proportion exist in human anatomy?
   - True
   - False.

10. Rule of Third is the face can be horizontally divided into thirds. From the hairline to the glabellar line (eyebrows) is 1/3, the brow to the base of the nose 1/3, and the base of the nose to the chin one-third.
    - True
    - False.

11. Rule of fifth uses width of the eye from corner to corner as a point of measurement; the face can be vertically divided into fifths. Starting from the very outside edge of one ear to the other the face ideally would be 5 eye widths apart. The width of the base of the would be a fifth.
    - True
    - False

12. The golden ratio is also known by many other names. Which of the following names is NOT one of those?
    - The golden mean
    - The golden integer
    - The golden number
    - The golden proportion.

13. The structure of which human body part is in accordance with Golden proportion?
    - Face
    - Lungs
    - Heart
    - All of Above.

14. Does Golden proportion influence Smile esthetics?
    - Yes
    - No
    - Don't Know.

15. Do you consider Golden proportion during any procedure?
    - Yes
    - No.

Advanced (A1) Category

16. What concepts should be considered while using Golden ratio as an aid for dental treatment?
    - Gender and age of patient
    - Understanding patient's desires and expectation
    - Concepts that create harmony between smile and facial esthetics
    - All of the above.

17. Which type of smile should be used to plan esthetic dental treatment?
    - Commissure smile
    - Cuspid or social smile
    - Complex smile
    - All of the above.

18. Which points must be considered while planning vertical changes of teeth in esthetic zone?
    - Occlusal maxillary plane and head inclination while assessing patient's smile
    - Mandibular function
    - Inter incisal angle
    - (a) and (c)
    - All of the above.

19. Which is the factor of paramount importance to achieve an attractive young smile?
    - Vertical positioning of maxillary incisors
    - Gingival design
    - Levels of gingival exposure
    - Tooth color and shape.

20. For clinicians to achieve ideal design of incisal contour in the esthetic zone, the step between central and lateral incisors must range from,
    - 1–1.5 mm for women and 0.5–1 mm for men
    - 0.5–1 mm for women and 1–1.5 mm for men
    - 0.5–1 mm for both
    - None of the above.

21. When viewed facially, the width of each anterior tooth is 60% of the width of the adjacent tooth.
    - Yes
    - No.

22. What is RED proportion?
    - Real Esthetic Dental proportion
    - Recurrent Esthetic Dental proportion
    - Recurring Esthetic Dental proportion
    - None of the Above.

RESULTS

Total 102 faculties from different fields have participated and filled the questionnaire form online. Out of 102, 58 were orthodontist and 44 were others (six prosthodontist, 24 general dentist, three oral and maxillofacial surgeons, and 11 others fields of dentistry). Since, the number of faculties other than orthodontists was small; they were grouped under "Others" category to compare with "Orthodontist" group.

According to years of experience, there is no statistically significant difference found in all three categories, rather, limited only to two questions where statistically significant difference is found in <5 years' experience (*P* value 0.018) and more than 10 years' experience (*P* value 0.032) [Tables 1 and 2]. These data do not resemble overall data so it is not to be considered to have any effect according to years of experience.

There are certain areas in which statistically significant difference is found between "Orthodontists" and "Others" regarding perception of Golden proportion in their respective fields. We have considered only those categories where minimum three questions are true from each participant, otherwise to be considered in false category [Tables 3-9].

Table 1: The Golden ratio is also known by many other names. Which of the following names is NOT one of those?

	False	True	Total
Years of Experience			
<5 years	17	11	28
5–10 years	32	6	38
More than 10 years	21	15	36
Total	70	32	102

Chi-square tests		
Chi-square value	**Df**	***P*-value**
6.872	2	0.032

Table 2: Do you consider Golden proportion during any procedure?

	False	True	Total
Years of Experience			
<5 years	4	24	28
5–10 years	18	20	38
More than 10 years	14	22	36
Total	36	66	102

Chi-square tests		
Chi-square value	**Df**	***P*-value**
8.362	2	0.018

Table 3: The Golden ratio is claimed to appear in many fields, such as cosmology, theology, arts, architecture, botany, and others

	False	True	Total
Area of Expertise			
Orthodontist	4	54	58
Others	14	30	44
Total	18	84	102

Chi-square tests		
Chi-square value	**Df**	***P*-value**
10.693	1	0.001

Table 4: The American mathematician, Mark Barr, has chosen Phi as the symbol for the Golden ratio. Phi is named after which of the following Greek sculptors?

	False	True	Total
Area of Expertise			
Orthodontist	29	29	58
Others	34	10	44
Total	63	39	102

Chi-square tests		
Chi-square value	**Df**	***P*-value**
7.880	1	0.005

Table 5: In what way is the golden ratio, phi, related to the Fibonacci sequence?

	False	True	Total
Area of Expertise			
Orthodontist	28	30	58
Others	36	8	44
Total	64	38	102

Chi-square tests		
Chi-square value	**Df**	***P*-value**
12.042	1	0.001

Here, B1 category is termed as basic question category, where it was found that "Orthodontists" had higher perception concerning golden proportion as compared to "Others" with statistically significant value of 0.001 [Table 10]. However, according to the survey of advance questions category (A1), "Orthodontists" do have higher perception than "Others" category, but this difference is not statistically significant.

DISCUSSION

The present study was performed to evaluate whether asymmetric and symmetric anterior dental discrepancies and extraoral profile discrepancies are detectable by various groups of evaluators, to how much extent they are having knowledge on concept of Golden ratio. The results of the present study demonstrated that the orthodontists possess a higher perception toward Golden ratio as compared to others. Orthodontist found Golden proportion to be very useful as it influences smile esthetics.

Researchers from varied areas have been motivated to study the possibility of facial-skeletal measurements to be related with the ideal proportions, such that the esthetics may be scientifically assessed rather than based on subjective judgments.[3-5] Snow[2] stated that symmetry, dominance, and proportion for an esthetically pleasing smile are the three composition elements required to create unity and esthetics in a smile and the concept of Golden percentage is a useful application in the diagnosis and development. Miller[6] stated that the trained and observant eye readily detects what is out of balance, out of harmony with its environment, or asymmetric. Investigation of lay people's self-perception of dental esthetics has focused largely on gross esthetic discrepancies

Table 6: Rule of fifth uses the width of the eye from corner to corner as a point of measurement; the face can be vertically divided into fifths. Starting from the very outside edge of one ear to the other the face ideally would be five eye widths apart

	False	True	Total
Area of Expertise			
Orthodontist	2	56	58
Others	13	31	44
Total	15	87	102

Chi-square tests		
Chi-square value	Df	*P*-value
13.585	1	<0.001

Table 7: Does Golden proportion influence of smile esthetics?

	False	True	Total
Area of Expertise			
Orthodontist	1	57	58
Others	9	35	44
Total	10	92	102

Chi-square tests		
Chi-square value	Df	*P*-value
9.926	1	0.002

Table 8: When viewed from facial, the width of each anterior tooth is 60% of the width of the adjacent tooth

	False	True	Total
Area of Expertise			
Orthodontist	8	50	58
Others	16	28	44
Total	24	78	102

Chi-square tests		
Chi-square value	Df	*P*-value
7.084	1	0.008

Table 9: What is RED proportion?

	False	True	Total
Area of Expertise			
Orthodontist	34	24	58
Others	34	10	44
Total	68	34	102

Chi-square tests		
Chi-square value	Df	*P*-value
3.917	1	0.048

Table 10: Area of Expertise* B1

Crosstab	B1		Total
	False	True	
Area of Expertise			
Orthodontist	0	58	58
Others	8	36	44
Total	8	94	102

Chi-Square Tests		
Chi Square Value	Df	P VALUE
11.443	1	0.001

Area of Expertise* A1

Crosstab	A1		Total
	False	True	
Area of Expertise			
Orthodontist	1	57	58
Others	4	40	44
Total	5	97	102

Chi-square tests		
Chi-square value	Df	*P*-value
2.913	1	0.088

related to debilitatingmalocclusions.[7-9] Few studies have evaluated anterior dental esthetics by investigating a person's perception of minor abnormalities.[10-15] Only one study has established threshold levels for several specific esthetic criteria that can be used readily by orthodontists, periodontists, restorative dentists, and oral and maxillofacial surgeons to aid in treatment planning.[16] However, aforementioned study evaluated symmetric esthetic alterations.

In reviewing the literature for Golden proportion, few studies have dealt with changes in facial esthetics. In one study, Barrer and Ghafari[17] assessed profile silhouettes before and after treatment, assessing these only as either "satisfactory" or "unsatisfactory." Lundstrom *et al*.[18] used orthodontists, orthodontic graduate students, laypeople, and artists to rate changes in facial esthetics in subjects from age 12 to age 18. They used a scoring system of 1–5, with 1 representing very attractive and 5 representing very disharmonious. Here, the change in esthetics was simply taken as the number of categories that each case moved up or down the scale. The same system was used by Kerr and O'Donnell.[19] Dunleavy *et al*. used a variety of judges to assess the effects of orthognathic surgery. In their study, pre- and post-treatment photographs were shown to the judges at the same time. Those subjects who were determined to show changes in appearance were ranked from most to least improved.[20]

CONCLUSION

Orthodontists gave higher perception regarding Golden proportion as compared to others with statistically significant value, but when we surveyed advance questions category (A1), orthodontists do have higher perception than others category, but this difference is not statistically significant.

This is a peer reviewed survey but this can be used a substantial approach for the patient to rate the same photos that were reviewed by the various specialties. This could result in a more educated and informed approach in the treatment of each patient.

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Original Article

Surgery for Chronic Pancreatitis and Different Methods of Surgeries

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Abstract

Background: Chronic pancreatitis, a benign inflammatory process of the pancreas and pain, is the most devastating symptom, for which patient seeks medical advice. It was a prospective study for 30 patients who were attended to our hospital and managed surgically during November 2020 to October 2021at our institute.

Materials and Methods: Data are collected and analyzed. Various surgical procedures for chronic pancreatitis and their indications are noted. Pain relief, improvement of exocrine and endocrine insufficiency, and improvement of quality of life are studied.

Results: Various operative procedures are done including intraoperative Celiac plexus block in some. Puestow's, Frey's, and Whipples PD are done in these patients, which are selected according to the pathological anatomy. We observed that long lasting pain relief is observed in 90% of our patients. In two of the patient's surgery was done in acute condition with edematous pancreas. In these cases, intraoperative celiac plexus block was added. Improvement in exocrine insufficiency was observed in eight individuals and improvement in endocrine insufficiency was observed in four persons.

Conclusion: Surgery is effective in chronic pancreatitis with intractable pain and better results can be obtained with selection of procedure tailor made to the patient. Exocrine and endocrine functions may become betted in some patients. Celiac plexus block is a useful adjunct to the surgery in selected group.

Key words: Chronic pancreatitis, Coeliac plexuses block, Frey's, Puestow's, Whipples

INTRODUCTION

Chronic pancreatitis is a progressive inflammatory disorder characterized as irreversible destruction of pancreatic parenchyma, associated with chronic pain, which is disabling and permanent loss of endocrine and exocrine function. Patients will present at a younger age with repeated attacks of severe pain abdomen, vomiting, steatorrhea, weight loss, and Type1 diabetes requiring insulin.

Recently, gene mutations associated with hereditary and idiopathic chronic pancreatitis have also been reported.[1]

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Patients come to the doctor with clinical symptoms such as maldigestion, severe weight loss, and recurrent severe upper abdominal pain. Later, in the course of the disease, endocrine and exocrine insufficiency may also develop.

The management for chronic pancreatitis is primarily of conservative and symptomatic treatment, but long-term follow-up studies showed demonstrated that about 50% of the patients might require surgical treatment at some time in their life.[2]

Recently, some studies showed that surgery has a positive impact on the course of chronic pancreatitis, in postponing the final "BURNOUT" of the pancreas and its consequent appearance of endocrine and exocrine insufficiency. Therefore, it should be of great clinical importance in the management of chronic pancreatitis to treat the above said problems surgically before the disease has progressed to an advanced stage in which the endocrine and exocrine function has lost completely.

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Mainly two different types of surgeries have been developed based on different pathogenesis of abdominal pain. The drainage type of surgery is based on the hypothesis of parenchymal and/or ductal hypertension.[2] The resection type approach is based on the hypothesis of perineuritis and local inflammatory. Drainage procedures include Puestow procedure, longitudinal pancreaticojejunostomy, pancreaticogastrostomy, and local resection procedures includes central pancreatectomy, distal pancreatectomy, duodenum preserving pancreatic head resection (Beger procedure), and proximal pancreatectomy – Whipple procedure or pylorus-preserving pancreaticoduodenectomy.

Aims and Objectives

The objectives of the study are as follows:

1. To study the age, sex distribution, etiology, and risk factors associated with chronic pancreatitis
2. To know the indication of surgery and type of surgery
3. To know the outcome and response of the surgical drainage procedure and resection procedure.

MATERIALS AND METHODS

Source of Data

All data were collected from the patients who presented with signs and symptoms of chronic pancreatitis to, Meenakshi Medical College Hospital and Research Institute, Kanchipuram, Department of General Surgery for treatment.

Design of the Study

It was a prospective study.

The clinical study of 30 cases of chronic pancreatitis was conducted by selecting cases presenting to Meenakshi Medical College Hospital and Research institute, Kanchipuram during a period of 2 years from November 2020 to October 2021.

Method of Collection of Data

All the patients with suspected chronic pancreatitis were investigated, offered individualized treatment, and followed up.

The institution where this study was conducted is equipped to carry out all necessary investigations, which helped in diagnosing and treating the cases.

These include an ultrasound scan, computed tomography, upper gastrointestinal endoscopy, ERCP, and barium meal which was immensely helpful in arriving at the diagnosis of chronic pancreatitis.

Plan for Data Analysis

The clinical outcomes were documented using a standard proforma. The collected data were analyzed by comparing them with various standard studies on chronic pancreatitis.

Inclusion Criteria

1. Patients with classical history and radiological characteristics of chronic calcific pancreatitis were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients with chronic calcific pancreatitis who are not willing to abstain from alcohol
2. Patients with poor performance status
3. Patient with pancreatic malignancy.

Investigation Details

- Blood investigations including CBC, liver function tests and RFT, CA 19-9, Viral markers.
- USG abdomen: To look for pseudocyst.
- Portal Doppler: To look for associated portal hypertension.
- UGI Scope: To look for extraneous impression and varices in cases of portal hypertension.
- CECT abdomen and pelvis: To look for calcification, head mass, stones in the duct and parenchyma, and diameter of the head and associated complications in the form of pseudocyst and perisplenic collaterals.
- CECT abdomen**:** CT-Angiography – To look for pseudoaneurysms around pancreas. MRCP and MRI – To look for the status of CBD in cases presenting with jaundice and cholelithiasis.

OBSERVATIONS AND RESULTS

Age Distribution

A total number of 30 patients who were diagnosed to have chronic calcific pancreatitis successfully managed were included in the study. The age of the patients varies from 15 to 58 years. The most of the patients were in their active earning period of life, 36–45 years [Table 1]**.**

Table 1: Age distribution

Age in years	No. of patients	Percentage
15–25	3	10
26–35	8	26.6
36–45	15	50
≥0.	4	13.3

Table 2: Sex distribution

Sex	No. of patients	Percentage
Male	25	83.3
Female	5	16.6

In our study, there were 25 (83.3%) male patients and 5 (16.6%) female patients out of 30, indicating that the disease is more common in males with a male to female ratio of 5:1 [Table 2].

Regarding the etiology of chronic calcific pancreatitis, alcohol was associated with 19 patients, and 11 patients were considered to be tropical [Table 3].

Clinical Presentation

Among the clinical presentations, all the patients were presented with abdominal pain, and the pain score was more than 8 for 18 patients and <8 for 12 patients. In addition to pain, the other clinical presentation are shown in [Table 4].

Table 3: Alcohol history

Cause	Number	Percentage
Alcohol	19	61
Non-alcohol	11	39

Table 4: Clinical presentation

Presentation	No. of patients	Percentage
Exocrine insufficiency	8	25
Endocrine insufficiency	4	13
Any complications (biliary obstruction, splenic vein thrombosis, duodenal obstruction)	-	-

Table 5: The morphological charecteristics

Findings	Number
Mpd dilatation	25
Mpd caliculi	20
Parenchymal calcification	5
Parenchymal atrophy	5
Inflammatory head mass	3
Abscess	1

Table 6: Surgical procedures

Name of the procedure	Number
Modified Puestow method	24
Freys procedure	2
Begers procedure	2
Whipples procedure	2

Table 7: Post-operative complications

Complications	Number
Wound infection	5
Atelectasis	3
Hepaticojejunostomy leak	1
Pancreatic leak	1
Delayed gastric emptying	1

Surgical Procedures

The patients have been chosen according to the diameter of the duct, presence of an inflammatory mass in the head region, and associated with other complications in the form of the pseudocyst, portal hypertension, and jaundice.

Post-operative Complications

As like any other surgeries, the complications following the surgical procedures for chronic calcific pancreatitis were,

Follow-up

In the immediate follow-up period, all the patients had pain relief drastically to the pain score of one and continue to be asymptomatic for a period of 6 months.

Three patients were readmitted with a recurrence of pain due to the resumption of alcohol. Patients with endocrine insufficiency had good glycemic control with a decreased dosage of insulin compared to the pre-operative dose of insulin, mainly in case of drainage procedure. Patients with exocrine insufficiency had improvement in steatorrhea, and there is weight gain postoperatively. The average pain score of the patient, which was 8 preoperatively, has come down to 1 in the immediate post-operative period.

Pain relief was more in case of inflammatory mass operated by freys procedure as it was believed that pain-sensitive is mostly located in the head of pancreas. Pancreatic insufficiency was slightly improved in patients subjected to the longitudinal pancreaticojejunostomy group. There is slight steatorrhea in case of resection procedures, especially in the case of Whipple's procedure and freys procedure.

Quality of Life

Although no formal instrument measuring the quality of life was used, quality of life after surgery was inferred from the results graded both by a degree of pain relief and activity status. The median number of hospital admission fell after surgery for all procedures from two admissions per year to none by 12 months after surgery, which was maintained during follow-up. There was a significant increase in those in regular employment after surgery. Twenty-eight of 30 (95.3%) patients rated as in good health were employed [Tables 5-9].

DISCUSSION

The therapy for chronic pancreatitis consists primarily of conservative and symptom-related treatment, but long-term follow-up studies have demonstrated that about 50% of the patients will undergo surgical treatment at some time in the course of the disease.

The main indication for the surgical treatment of chronic pancreatitis is to alleviate severe pancreatic pain and to

Table 8: Incidence of alcohol abuse and results of surgery after pancreaticojejunostomy for chronic pancreatitis

Study	Year	Number	Alcohol abuse	Operative mortality	Late deaths	Relief of pain
Greenlee *et al*.	1990	100	100	(4)	3 (3)	75
Hakaim *et al*.	1994	50	60	0 (0)	5 (10)	89
Sharma *et al*.	1998	58	0	4 (7)	4 (7)	99
Present study		30	19	0 (0)	0 (0)	28

Table 9: Comparison of morbidity after surgery with Izbicki *et al*. and current study.[8]

	Present study Number-Percentage	Izbicki *et al*.[8] Number-Percentage
MORBITY	3/30-10%	6/45-13.3%

manage pancreatitis-related locoregional complications, improve the quality of life by decreasing the intensity and repeated attacks of pain, and also in improvement in the exocrine and endocrine function of the remaining pancreas in case of chronic pancreatitis. According to the conventional wisdom, an operative procedure for chronic pancreatitis, as a palliative measure on an already functionally impaired gland, it should be as conservative as possible to limit the occurrence especially of endocrine failure. Out of six, five had the most relief of pain. Longitudinal pancreaticojejunostomy (LPJ) is safe because it preserves gland there less incidence of exocrine and endocrine deficiency in patients postoperatively.

We had no post-operative death with LPJ (mortality 0%). Many authors have reported a low mortality rate (0 %). During follow-up, no patients died at a mean of 13 months after the operation, which is comparable with the reported rate. Pain relief was classified as good in 27 of 30 patients (90%) who underwent surgery for intractable pain.

Etiology-alcohol

In our study, among the alcoholic chronic pancreatitis, 2 of 19 patients (20%) continued to consume alcohol. Lankisch *et al*. and Layer *et al*. demonstrated that only 13–20% of deaths in patients with chronic pancreatitis are directly related to pancreatitis.[3]

In our study, the type of surgery or the etiology of chronic pancreatitis did not influence the long-term outcome of a patient with chronic pancreatitis.

Pain Relief

In our study, operative therapy not only led to long-lasting pain relief in the majority of patients operated but also resulted in a significant increase in the proportion of patients able to work or function normally in society from 9% to 82%, according to a better quality of life.

Although a higher proportion of patients with tropical chronic pancreatitis patients had pain relief following surgery, we did not find any correlation between pain relief in alcoholic pancreatitis and those who were not alcoholic. This result was similar to the report reported by Brinton *et al*.[4] who reported results of lateral pancreaticojejunostomy in 39 patients This is, in contrast, to a report by Sato *et al*., who found that over a mean period of 9.1 years, only 50% of patients with alcoholic pancreatitis had a good result after surgery compared to 83% of those who had non-alcoholic pancreatitis.[5]

Endocrine and Exocrine Insufficiency

The operation resulted in an improvement of the patient's diabetic status, with about 3 of 4 patients (75%) who were dependent on a high dose of insulin before surgery being taking a low dose of insulin, and euglycemic status was achieved. Exocrine pancreatic dysfunction was improved in 75% of patients who had steatorrhea preoperatively. Similar experiences have been reported from India in patients with tropical calcific pancreatitis. Sidhu *et al*. have shown that there was a significant improvement of endocrine insufficiency and slight improvement of exocrine insufficiency in patients with tropical chronic pancreatitis undergoing modified Puestow procedure in a long-term follow-up study.[6] In our study, there was no difference in pancreatic insufficiency between and resection group, which is similar to a report from Mayo clinic study by Sakorafas *et al*.[7]

Coeliac Plexuses Lock

Coeliac plexuses block is particularly useful in case of not much dilated pancreatic duct. Adding celiac plexus neurolysis to the current standard procedure in a single sitting as a part of multimodal approach will provide additional benefit to the patient not only by improving the psychological well-being but also by reducing the opioid intake thereby leading to a better quality of life various studies and RCTs on celiac plexus block also have shown to improve QOL in both chronic pancreatitis.[8]

Quality of Life after Surgery in Chronic Pancreatitis

The EORTC-QLQ has now been applied in two prospective and randomized trials comparing surgical techniques in patients with chronic pancreatitis, which stress the

draining or the resectional aspects of treatment to varying degrees.[8,9] Statistically significant changes in symptoms and functional levels were observed. In both trials, the patients' overall quality of life improved considerably. Relief of symptoms, especially of pain, fatigue, and loss of body weight, accounted for the improvement of physical status, working ability, and emotional and social functioning.[10]

Post-operative Complications

In our study, one patient who undergone Whipple's surgery for chronic pancreatitis had hepaticojejunostomy leak on POD5. We managed the patient by repeated aspiration of a collection in the peritoneal cavity by ultrasound aid. The leak came down in 5 days. Another patient who has also undergone Whipple's had a pancreatic leak from the pancreaticogastrostomy anastomosis. She was managed by strict NBM and ryles tube aspiration. As the fistula was low output fistula, it resolved in 5 days.

Morbidity and Mortality

Lateral pancreaticojejunostomy is a relatively safe procedure despite its magnitude. The post-operative morbidity rate of 13.3% was within an acceptable range.

Association with Pancreatic Cancer

Preclinical epidemiologic and studies demonstrate that chronic pancreatitis is associated with the development of pancreatic cancer. Maisonneuve and Lowenfels[11] presented a multicentre historical cohort study of 2015 patients with chronic pancreatitis followed for at least 2 years. The standardized incidence risk ratio for the development of pancreatic cancer was 16.5 and 14.4 at 2- and 5-year follow-up, respectively, for the risk of developing pancreatic cancer. However, in our study, we have excluded the cases with pancreatic malignancy changes.

CONCLUSION

Operative management of CP, when indicated, can be done safely with good results in terms of relief of abdominal pain, weight gain, and quality of life. Significant improvement in pancreatic exocrine insufficiency and endocrine insufficiency after surgery can be expected. Resectional procedures will have higher early morbidity. Unsuspected and unnoticed malignancy is a common etiology for late deaths. Continued use of alcohol intake is associated with poor pain relief and quality of life. Biomarkers are needed for early identification of CP and assessment of abdominal pain, as well as and robust databases and epidemiological studies to better define chronic pancreatitis and predict its outcomes. At the same time, better means are needed to measure the exocrine pancreatic function in a reliable, non-invasive, and reproducible manner.

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Original Article

Antibiogram of Uropathogens Isolated in Microbiology Laboratory of Indoor and Outdoor Patients including Occurrence of Yeast Infections in COVID-19 Patient

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Abstract

Background: Urinary tract infection remains one of the most common infections, both in the community and in the hospital. The pathogen profile is mostly common with slight variations, but *Escherichia coli* remains the most common causative pathogen. The sensitivity of uropathogens to different drugs varies in different areas and changes with time. This necessitates periodic studies of the causative uropathogens and their antibiotic sensitivity pattern.

Materials and Methods: This is retrospective, descriptive, and observational study. Duration of study was for 6 months from January to June 2021. All positive urine culture during the study period in the department of microbiology. The study was conducted in Microbiology Department of ESI-PGIMS and ESIC Medical College, Joka, Kolkata, West Bengal.

Results: Out of 949 urine samples received, 242 (25.5%)were found to be positive for uropathogens. Among the received samples, 133 (54.9%) were inpatient whereas outpatient was 109 (45.04%). Prevalence of UTI was higher in female 175 (72.3%) and among males, it was 67 (27.6%). Significant bacteriuria was seen in 201 (83.05%) patients and 10 (4.13%) patients had an insignificant colony count. Mixed growth was seen in 8 (3.30%) samples and 25 (10.3%) samples showed growth of *Candida* spp.

Conclusion: *E. coli* is the most likely organism grapple with UTI and the most of the strains of *Enterobacteriaceae* isolated from a hospital are multi drug resistant. Few pan-resistant strains of *Klebsiella* spp. are alarming.

Key words: Antibiogram, Bacteria, Infection

INTRODUCTION

Urinary tract infections (UTIs) are among the most common bacterial infections. UTIs are the inflammatory disorders caused of invasion of urinary tract by the abnormal microbial growth.[1,2] Common symptoms of UTI are fever, dysuria, and lower abdominal pain and it may result in permanent scarring of the kidney.[1,2] UTIs depending on source of infection are of two types: Community acquired or nosocomial. Community-acquired UTIs (CA-UTIs) are defined as the infection of the urinary system that takes place in one's life in the community setting or in the hospital environment with <48 h of admission.[3] CA-UTI is the second most common microbial infection in the community setting. Nosocomial UTIs are the infection of the urinary tract that occurs after 48 h of hospital admission, and the patient was not incubating at the time of admission or within 3 days after discharge.[5] Irrational antibiotics use with increased consumption and inappropriate prescribing and lack of regulations to the availability of antibiotics over the counter which promotes overuse are important causes for increased bacterial antibiotic resistance.[6] There is widespread dissemination of the over the counter of nearly all antibiotics without medical prescription and overuse.[3-6]

Hence, with this background, the present study aimed at investigating the bacterial agents responsible for UTIs in a tertiary care hospital setting and study their antibiotic susceptibility pattern.

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MATERIALS AND METHODS

Duration of Study

The duration of the study was 6 months, from January to June 2021.

Sample Size

All urine culture with significant growth, during study period were include.

Place of Study

This study was conducted at Microbiology Department of ESI-PGIMS and ESIC Medical College, Joka, Kolkata, West Bengal.

Type of Study

This was a retrospective, descriptive, and observational study.

Inclusion and Exclusion Criteria

All positive samples with colony counts yielding bacterial growth of 10^5/mL of urine were regarded as significant for bacteriuria. Symptomatic cases with a lower count were also considered for the study.

Exclusion Criteria

No growth and asymptomatic cases with insignificant counts were excluded from the study.

Study Variables

Age, sex, indoor or outdoor patient, COVID status, any other related underlying condition.

Laboratory Methods

Urine culture will be done by a semi-quantitative method on Hi-chrome media and isolation of yeast on Chrome Agar.[7] Using calibrated inoculating loop 0.001 Ml[4] of uncentrifuged, uniformly mixed, midstream urine samples were aseptically inoculated onto Hi-chrome agar. After overnight incubation at 37°C for 24–48 h, colonies were counted to check significant growth.[8] Identification of bacteria was done using standard microbiological procedures.[7,8] The samples were cultured on Chrome agar. After macroscopic and microscopic observation of yeast cells; for confirming the species of *Candida albicans*, the samples were transferred into human serum for 3 h to grow the germ tubes.[9] The observation of germ tubes in Candida yeast cells was the most important physiological property to report the yeast cells as *C. albicans*.[9]

Significant candiduria was determined as urine culture growth $\geq 10^4$ CFU/ml. All significant candiduria were identified microscopically for morphological characteristics using germ tube production test.[10-12] All positive urine cultures with significant bacteriuria were further identified by their colony characteristics, Gram-stain, and pattern of biochemical profiles using standard procedures.[7,9] Antimicrobial susceptibility testing was done by the modified Kirby Bauer disc diffusion method and Vitek according to the Clinical Laboratory Standards Institute (CLSI) guidelines.[13] An attempt was made to study ESBL production and multiple drug resistant in isolates.[14]

Antimicrobial Susceptibility Testing

Antibiotic susceptibility test was carried out on each isolated bacteria using Kirby Bauer disc diffusion method according to the CLSI: M100-S22 guidelines.[14 Bacterial suspensions were prepared by emulsifying 3–5 pure colonies in nutrient broth and adjusted to 0.5 McFarland standards. A sterile cotton swab was then dipped into the suspension and swabbed on surface of Mueller-Hinton agar plate. Standard antibiotic discs were placed aseptically, and the inoculated Mueller Hinton agar plates were incubated at 37°C for 24 h.[7] The diameters of the zones of complete inhibition were measured using mm of calipers. The isolate zone of inhibition was reported based on CLSI M100-S22 standard as Susceptible, Intermediate, and Resistant.[9] The following antibiotic discs were tested for the isolates: Ampicillin (10 μg), Amoxicillin-Clavulanic acid (10 μg), Ceftazidime (30 μg), Ceftriaxone (30 μg), Gentamicin (10 μg), Nitrofurantoin (300 μg), Cefotaxime (30 μg), Trimethoprim Sulphamethoxazole (1.25 μg), Ciprofloxacin (5 μg), Tobramycin (10 μg), Amikacin (30 μg), Penicillin (10 unit), and Vancomycin (30 μg).

Species Identification and Antibiotics Susceptibility

Species identification of Gram-positive bacteria and Gram-negative bacteria (GNB) and antibiotics susceptibility testing was determined with VITEK® 2 compact system (bioMérieux, France) using GN, GP, AST-235, AST-280, and AST-281 cards.[9] The investigated antibiotics by VITEK® 2 cards were the following: Piperacillin, piperacillin/tazobactam (PIT), ceftazidime, cefepime, aztreonam, imipenem, meropenem, amikacin, gentamicin, netilmicin, tobramycin, ciprofloxacin, levofloxacin, tetracycline, tigecycline, trimethoprim/sulfamethoxazole (COT), fosfomycin, nitrofurantoin, benzylpenicillin, erythromycin, clindamycin, linezolid, daptomycin, teicoplanin, and vancomycin. Isolates with resistance or intermediate susceptibility were considered non-susceptible to the antibiotic agent. The results were interpreted according to the 2015 CLSI criteria.[9]

Quality control: Sterility and performance of culture media were tested before using the culture media. Standard reference strains of *Escherichia coli* (ATCC 25922) and *Staphylococcus aureus* (ATCC 25923) were used as control for culture and sensitivity testing.

Statistical Analysis

The analysis of data obtained from this study was done using SPSS statistical software package (version 20). Percentage and frequency were used to show distribution of descriptive data using tables.[14] Bi-variable and multi-variable analyses were done using logistic regression model for the outcome variable (significant culture positivity) and independent variables (sociodemographic characteristics and health related factors) for further interpretation based on the odds ratio and level of statistically significant at $P < 0.05$. In addition, Chi-square test was employed to see the association between current UTI status and uropathogen growth.[14]

(ESBLs) are a large group (>150) of β-lactamases that confer resistance to the oxyimino-cephalosporins and monobactams. The Vitek-2 ESBL test is based on a comparison of the inhibitory effects of ceftazidime, cefotaxime, and cefepime, alone and in combination with clavulanate. The Vitek-2 ESBL test is an efficient automated test that allows accurate detection of ESBL production, and it is, therefore, potentially useful for clinical microbiologists.[13]

RESULTS

Out of 949 urine samples received, 242 (25.5%) were found to be positive for uropathogens. Among the received samples, 133 (54.9%) were inpatient whereas outpatient were 109 (45.04%). Prevalence of UTI was higher in female 175 (72.3%) and among males, it was 67 (27.6%). Significant bacteriuria was seen in 201 (83.05%) patients and 10 (4.13%) patients had an insignificant colony count. Mixed growth was seen in 8 (3.30%) samples and 25 (10.3%) samples showed growth of *Candida* spp.

Age and Gender Wise Distribution of Patients

The most of the cases were recorded in 15–45 (41.9%) years of age group followed by 65–90 (29.4%) years. In both age groups, females showed higher risk of developing UTI than male. Age/sex-wise distribution is given in [Figure 1].

Pregnancy (36.3%) was the most common factor associated with UTI, followed by diabetes mellitus (17.3%). Renal disorder and catheterization was present in 14.7% of the study subjects, others (12.5%) include patients in reproductive age group without any other complication [Figure 2].

E. coli was the predominant organism (45%) and second most common organism isolated was *Klebsiella* species (16%) and third most common organism was *Enterococci* species (11%) followed by *Pseudomonas* species (10%). *Candida* species was (7%), *Acinetobacter* spp. (4%), *S. aureus* (3%), mixture (3%) [Figure 3].

E. coli was statistically associated more with Community Acquired-UTI and *Klebsiella* spp. was statistically associated more with hospital acquired-UTI.

In our studies, Carbapenem group of drugs was most effective against members of *Enterobacteriaceae*. Cephalosporins and aminoglycosides showed maximum

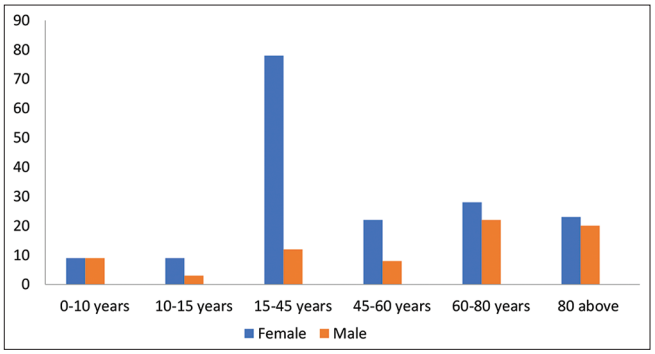

Figure 1: Age/Sex-wise distribution of patients with UTI

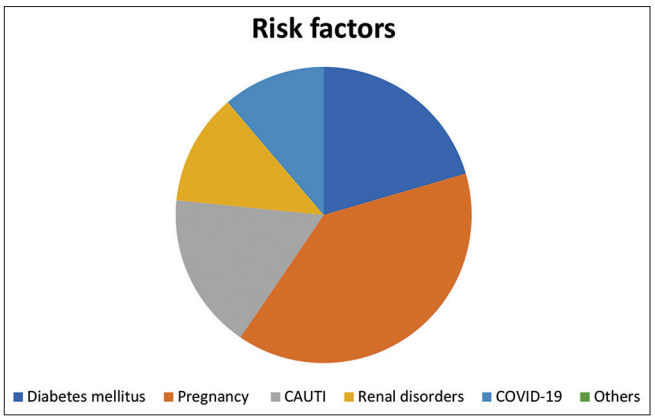

Figure 2: Risk factors associated with UTI in our study

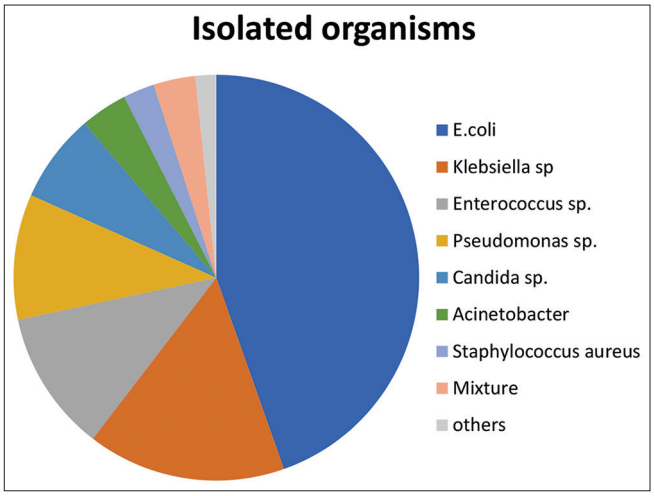

Figure 3: Organisms associated with UTI in our study

resistance. Quinolones showed sensitivity in 76% of patients. Drugs such as Fosfomycin and Colistin also were presented with resistance. About 7.1% (11) of *Enterobacteriaceae* were pan-resistant [Figure 4].

Vitek-2 ESBL detection-The Vitek-2 ESBL test identified 86 (56.2%) of the 153 *Enterobacteriaceae* isolates. Sixty-three (41.1%) *E. coli* and 23 (14.7) *Klebsiella* spp. isolates were ESBL producers. ESBL-producing isolates also carried genes for at least one broad-spectrum beta-lactamase (e.g., TEM-1/2, SHV-1, and SHV-11).

The VITEK 2 ESBL test is a new tool for rapid detection of ESBL production which is based on simultaneous assessment of the inhibitory effects of cefepime, cefotaxime, and ceftazidime, alone and in the presence of clavulanate.

The third most common isolated organism was *Enterococci* spp. showed maximum sensitivity toward Vancomycin (90%), Linezolid (86.2%), Gentamicin (75.0%), and maximum resistance to fluroquinolones (50%). Vancomycin resistance was detected in 10%.

This study also followed urinary yeast infection, the yeast was identified according to different characteristics such as their macroscopic, microscopic, and physiological properties.

A total of 17 patient (7%) were detected with Candiduria, all of these were in prolonged hospitalization due to complication of COVID-19.

RESULTS

UTI is one of the infectious diseases, it is both community and hospital acquired. Incidence of UTI in this region and all over India ranges between 44.5% and 58.6%,[14-19] incidence in our study was 25.5% which was lower than the other studies. The reason for lower incidence is since study population is mostly urban[15] and during the duration of study second wave COVID-19 pandemic occurred, therefore, leading to reduced footfall in hospitals.[20]

In our study, we established a high prevalence of UTI in females (72.3%) than in males (27.6%) which is accordance with other findings which also revealed the similar results.[15-19] The association behind this high prevalence of UTI in females may be due to proximity of the urethral meatus to the anus, shorter urethra, sexual intercourse favoring the entry of bacteria into urethra and other common reasons are incontinence, and pregnancy.[21-23] In reproductive age group females (15–49), the susceptibility of UTI was higher (84.3%) followed by 65–90 years (82.93%). These findings are like other reports which showed that females are more prone to UTIs than males during adolescence and old age.[15-17] Increased association of UTI in young age females is due to sexually active behavior, pregnancy, recent use of a diaphragm with spermicide, and a history of recurrent UTIs in elderly female, it is due to reduced vaginal acidity and fleeting defense mechanism.[15,17,21]

Diabetes mellitus is associated with hyperglycemic urine, which promotes rapid bacterial growth and colonization.[2] Pregnancy also showed high association with UTI (36.3%) among females. Manjula *et al.* in Bangalore reported 49.9% incidence of UTI in their study.[18] The bladder tonein is reduced due to hormonal change. Pregnancy produces physical obstruction in the female urinary tract,[22,23] catheterization appeared as common risk factor for UTI in this study. For either short- or long-term catheters, the infection rate was 14.7%. Infection spreads by biofilm

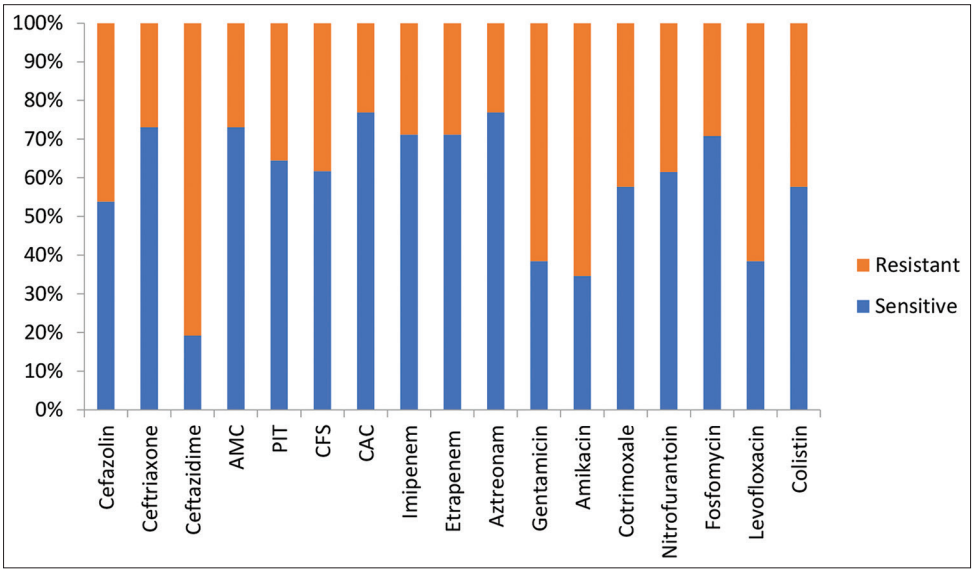

Figure 4: Antibiotic sensitivity pattern for members of *Enterobacteriaceae* (*n* = 153)

formation on both internal (intraluminal route) and external (periurethral route) catheter surface.[16,18]

In our study, we also followed cases of yeast infection. Prolonged hospitalization, immuno-compromised patients, uncontrolled use of antibiotics, prophylaxis by antifungal agents, catheterization, urinary tract surgeries, and long period stays in intensive care units were some of the leading causes associated with fungal urinary infections.[4,9,25] During the study period, there was a surge in COVID-19 cases leading to prolonged hospitalization, immunocompromization, overuse of antibiotics.[25,26] A total of 7% cases were diagnosed with Candiduria. The most important uropathogen causing candiduria was *C. albicans*. Many contributing factors of *C. albicans* virulence are adhesion, hyphal formation, phenotypic switching, extracellular hydrolytic enzyme production, and biofilm formation.[9]

The prevalence of uropathogens in our study are in sync with a few studies conducted in the country.[5,16-21] *E. coli* was the most common cause of UTI in every study, we referred during writing this article.[16-20] We isolated *E. coli* in 45% of cases, which matches with other studies done in same geographic region. The factor associated with highest prevalence of *E. coli* is that it is present in normal fecal flora, and it colonize in the uroepithelium with the assistance of adhesins, pili, fimbriae, and P1-blood group phenotype receptor.[2]

Second highest association was shown by *Klebsiella* species (16%) which agrees with many other studies from India.[27,28]

In our study, 11% of the isolates were *Enterococcus* spp. According to study of Kaushik *et al.* from Karnataka, *Enterococci* spp. accounted for 11.7% of urinary tract isolates.[2]

Overall, among the Gram-negative uropathogens, high resistance pattern was noted for ampicillin, third generation cephalosporins. Aminoglycosides also showed moderate-to-high resistance.

Earlier, commonly used drug combinations such as PIT, Cefoperazone/Sulbactam Ceftazidime/clavulanate, Amoxicillin/Clavulanic acid AMC showed high resistance, this is in contradiction to the studies[16,18,19] done before 2015 but these result matches studies done in recent times.[17] This hints toward growing MDR, ESBL in GNBs. This could be due to the overuse use of these antibiotics. In this study, the most useful antibiotic for Gram-negative uropathogens was Carbapenems, Nitrofurantoin, Quinolones, and Fosfomycin. We observed that resistance toward Fosfomycin and Colistin is in upward trends. Similar resistance patterns are observed by other authors in their respective studies. Raising number of Pan-resistant *Klebsiella* spp. infections in Hospital acquired UTIs is an alarming situation.[29] Pan-resistant Enterobacteriaceae infections are a menace observed in many other similar studies.[30] *Enterococci* spp. showed maximum sensitivity toward Vancomycin (90%) followed by Linezolid (86.2%), Gentamicin (75.0%), and maximum resistance to fluroquinolones (50%). Vancomycin resistance (VRE) was detected in 10% of *Enterococci*. Emergence of VRE is mentioned few other studies.

CONCLUSION

Our study stating that *E. coli* is the most likely organism grapple with UTI and the most of the strains of *Enterobacteriaceae* isolated from a hospital are multidrug resistant. Few pan-resistant strains of *Klebsiella* spp. are alarming. Empirical therapy for GNB can be started with Aztreonam, Ertapenem, or PIT or nitrofurantoin. In Gram-positive cocci cases, vancomycin or linezolid can be used. In view of the increasing drug resistance, antimicrobial susceptibility should be done, before starting therapy. Another cause of concern was increasing Candiduria cases, especially in hospitalized patients with immunocompromization.

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Original Article

A Retrospective Study on Demographic Characteristics, Response, and Survival of Unresectable or Metastatic Gallbladder Cancer Patients Treated with Chemotherapy

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Abstract

Introduction: Gallbladder cancer (GBC) is the most common biliary tract malignancy worldwide. It arises from the epithelial lining of the gallbladder or the cystic duct. It manifests either as a gallbladder wall thickening or a mass lesion in the fundus, body, or neck of the organ. Other biliary tract malignancies include intrahepatic and extrahepatic cholangiocarcinoma. In most of the clinical trials, these entities have been clubbed together as one disease and treated similarly. GBC represents 80–95% of biliary tract cancers worldwide, according to autopsy studies.

Materials and Methods: The present study was single-institution retrospective cohort study. This study was conducted from January 1, 2017, to June 31, 2020, at Apollo Multispecialty Hospitals Ltd., Kolkata.

Results: In our study, 61.3% of patients had gallbladder stone and 38.7% did not. We documented gallbladder stone in our study population from a history or baseline imaging study. Our study revealed a lower proportion of gallbladder stone associated with cancer which was probably because a majority of GB stones are radiolucent and hence missed on X-ray-based imaging like computed tomography scan.

Conclusion: Overall response rate and progression-free survival to second-line chemotherapy were 37.5% and 2.85 months, respectively. Some of the patient and disease characteristics such as low body mass index, poor performance status, and metastatic disease adversely affected survival.

Key words: Computed tomography scan, Extrahepatic and carcinoma, Gallbladder cancer

INTRODUCTION

Gallbladder cancer (GBC) is the most common biliary tract malignancy worldwide. It arises from the epithelial lining of the gallbladder or the cystic duct. It manifests either as a gallbladder wall thickening or a mass lesion in the fundus, body, or neck of the organ. Other biliary tract malignancies include intrahepatic and extrahepatic cholangiocarcinoma. In most of the clinical trials, these entities have been clubbed together as one disease and treated similarly. GBC represents 80–95% of biliary tract cancers (BTCs) worldwide, according to autopsy studies.[1] The global rates for GBC exhibit striking variability, reaching epidemic levels for some regions and ethnicities. In most instances, GBC develops over 5–15 years, when metaplasia progresses to dysplasia, carcinoma *in situ*, and then, invasive cancer. Progression is frequently rapid and silent, portending an abysmal prognosis. The dismal prognosis, in part, relates to the gallbladder lacking a serosal layer adjacent to the liver, enabling hepatic invasion and metastatic progression. Silent in its infancy, this malignancy remains asymptomatic until aggressive disease has progressed to an advanced and non-curative stage. It is either detected incidentally at the time of cholecystectomy or when it presents with complications due to local spread of the malignancy in the form of jaundice, hepatomegaly, ascites, or duodenal

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obstruction. A satisfactory outcome depends on an early diagnosis and surgical resection. Despite this potential for cure, <10% of patients have tumors that are resectable at the time of surgery, while nearly 50% have lymph node metastasis. Even after surgery, most progress to metastatic disease, highlighting the importance of improving adjuvant therapies.[2] Advanced, unresectable, or metastatic disease is incurable and usually treated with palliative chemotherapy. However, even with chemotherapy, the median survival has failed to go beyond a year. There is no salvage chemotherapy regimen approved so far. Hence, there is an unmet need to develop newer strategies in this patient group to improve outcome.

Vague abdominal symptoms often mask a more worrisome diagnosis contributing to its overall progression and poor outcome. Patients with GBC may present with a number of nonspecific complaints, such as anorexia and weight loss, as a precursor to jaundice. Imaging can detect malignancy. Ultrasound, readily available, might reveal a polypoidal gallbladder mass and perhaps invasion of adjacent structures. Incidental findings include the presence of cholelithiasis and calcification, in the form of the porcelain gallbladder. Wall thickness (>3 mm) and enhanced vascularity are sonographic features that can also signify potential malignancy.[3] Computerized tomography (CT) helps identify any extension to lymph nodes, liver involvement, or distant metastases. Fluorodeoxyglucose positron emission tomography (PET) scanning captures the uptake of fluorodeoxyglucose by tumor cells. PET scans are useful in differentiating malignant from benign disease. Based on three well conducted randomized controlled trials, the current standard of care for advanced GBC (A-GBC) is a gemcitabine-platinum doublet which entails a median survival of 9.5–11.7 months.[4] The first trial that established the doublet therapy was the ABC-02 trial which cemented the place of gemcitabine-cisplatin combination chemotherapy in the first-line setting. The combination of gemcitabine and oxaliplatin (GEMOX) has shown promising activity in this setting as well. An international Phase II study evaluated the efficacy and safety of GEMOX as first-line therapy in patients with advanced BTCs. In this study, GEMOX, albeit, demonstrated activity in non-gallbladder BTCs, but poor activity in gallbladder carcinoma.[5]

Aims and Objectives

The aim of the study is to evaluate the demographic characteristics of the patients and their response to treatment and survival and also analyze the various palliative chemotherapy regimens used in the 1st and 2nd line setting of unresectable or metastatic carcinoma of gallbladder in terms of response rate, progression-free and overall survival.

Objectives

Demographic characteristics

The objectives of the study were to evaluate demographic characteristics of patients with unresectable or metastatic carcinoma of gallbladder.

Response rates

The objectives of the study were to calculate response rates of patients with unresectable or metastatic carcinoma of gallbladder treated with chemotherapy.

Progression-free survival (PFS)

The objectives of the study were to analyze PFS in patients with unresectable or metastatic carcinoma of gallbladder after being treated with the 1st or 2nd line chemotherapy.

Overall survival

The objectives of the study were to analyze overall survival of patients with unresectable or metastatic carcinoma of gallbladder treated with palliative chemotherapy.

MATERIALS AND METHODS

Study Site

Apollo Multispecialty Hospitals Ltd., Kolkata (formerly, Apollo Gleneagles Hospital, Kolkata).

Study Population

Patients diagnosed with unresectable or metastatic gallbladder cancer, who received palliative chemotherapy in the Department of Medical Oncology in Apollo Multispecialty Hospitals Ltd., Kolkata (formerly, Apollo Gleneagles Hospital, Kolkata).

Study Design

This was a single-institution retrospective cohort study.

Study Period

The study period was from January 1, 2017, to -June 31, 2020.

Inclusion Criteria

The following criteria were included in the study:

- Patients with histopathology or cytology-proven diagnosis of gallbladder carcinoma
- Patients with unresectable or metastatic disease – Stages III (inoperable)-IV disease by AJCC TNM staging with appropriate imaging as per clinical practice
- Age ≥18 years
- Patients who are either treatment naïve or did not receive more than 1 line of chemotherapy
- Patients who received chemotherapy (at least one cycle) at Apollo Hospital, Kolkata.

Exclusion Criteria

The following criteria were excluded from the study:

- Those who received chemotherapy or targeted therapy elsewhere
- Those who received radiotherapy with curative intent
- Those who have hyperbilirubinemia (serum bilirubin over 3 mg/dl).

Statistical Analysis

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analyzed by SPSS 24.0 and GraphPad prism version 5. A Chi-squared test (χ^2 test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a Chi-squared distribution when the null hypothesis is true. Without other qualification, "Chi-squared test" often is used as short for Pearson's Chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. $P \leq 0.05$ was considered for statistically significant.

RESULTS AND DISCUSSION

The aim of this study was to acquire knowledge about the demographic characteristics of the patients afflicted with unresectable or metastatic gallbladder cancer who came for treatment at our institute.

Body Mass Index (BMI)

BMI is a statistical index using a person's weight and height to provide an estimate of body fat in males and females of any age. The National Institute of Health (NIH) now uses BMI to define a person as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2).[6] Baseline BMI of all patients was calculated from height and weight documented on the day of administration of first cycle chemotherapy. They were then classified into the above-mentioned four groups. Various studies from India, mostly of case–control design, revealed that patients with GBC have lower BMI compared to their healthy counterparts. In our study, 85.5% of patients had a BMI of <30 kg/m^2 while only 14.5% of patients were obese. This finding is at par with the figures found in various Indian series. Low BMI is generally a surrogate for poor or malnutrition, which may be associated with suboptimal immune status and a pro-inflammatory state secondary to micronutrient and antioxidant deficiency; both of which, in turn, can promote malignancy. In our study, only 6 patients (9.6%) were underweight. Being a tertiary care private institution, usually patients from medium to high socioeconomic strata are treated here. Hence, this low incidence of underweight patients in our study population may not be representative of the true picture prevailing in the country.

Gallbladder Stone

Various studies in India have documented presence of gallstone in 70–90% of patients with GBC. Certain studies have a lower rate, possibly due to problems with detecting them on ultrasound when they are entrapped within a mass. Another reason is that most gallstones are radiolucent and they may or may not be picked up on CT scan.

In our study, 61.3% of patients had gallbladder stone and 38.7% did not. We documented gallbladder stone in our study population from a history or baseline imaging study. Our study revealed a lower proportion of gallbladder stone associated with cancer which was probably because a majority of GB stones are radiolucent and hence missed on X-ray-based imaging like CT scan. Even with this limitation in documentation of gallstones in our patients, our percentage of gallstones (61.3%) was close to the Indian data (70%).

Treatment Received 1st Line Chemotherapy

In the first-line setting, patients received a variety of chemotherapy regimens. Of the 62 who received chemotherapy, majority of patients (56.5%) got gemcitabine plus cisplatin regimen. The second most common regimen was gemcitabine plus oxaliplatin (17.7%). About 14.5% of patients received gemcitabine monotherapy. Others received gemcitabine plus carboplatin, gemcitabine plus capecitabine, and gemcitabine plus nab-paclitaxel. Only one patient received non-gemcitabine-based chemotherapy with capecitabine.

PFS to 1st Line Chemotherapy

Median PFS was 5.33 months (0.2–34.8) in our study. Gemcitabine monotherapy produced a median PFS of 2.87 months. Gemcitabine plus cisplatin doublet showed a median PFS of 5.43 months while the third group where patients received gemcitabine doublets other than with cisplatin had a median PFS of 6.73 months. The difference was statistically significant. Hence, gemcitabine-based doublet is significantly superior to gemcitabine monotherapy in terms of PFS. In our study, patients who received gemcitabine in combination with platinum agents (cisplatin, carboplatin, or oxaliplatin) showed significant improvement in PFS over those who did not (6.73 months vs. 2.87 months). In the ABC 01 trial, median progression-free survival was 8.0 months in the cisplatin plus gemcitabine group and 5.0 months in the gemcitabine-only group. A small study[7] was undertaken to evaluate the efficacy and safety of combined chemotherapy of gemcitabine and carboplatin in 20 patients. The median time to progression of the tumor was 33.8 weeks or 7.8 months. To sum up, PFS to first-line chemotherapy in A-GBC is approximately 8 months with doublet chemotherapy and 5 months with gemcitabine monotherapy. In our study, the PFS was on the

lower side due to a few reasons. First, the study population received a variety of chemotherapy regimens from single-agent therapy to doublet chemotherapy. Second unlike the clinical trials, we included a number of patients who had a performance status (PS) of ECOG 2. Patients with poor PS who had poor prognosis from the outset brought down collective PFS of the whole study population.

Overall Response Rate (ORR) to 2nd Line Chemotherapy

ORR was 37.5%. There was no complete response. Progressive disease was seen in 8 patients (50%). In 2 patients (12.5%), the disease was stable. Six patients (27.3%) could not be evaluated for response as they died even before the first imaging study could be done after start of 2nd line chemotherapy. ORR in our study was slightly higher than what we find in literature. Of the six patients who showed partial response, four had received capecitabine plus oxaliplatin (CAPOX) chemotherapy. The other two responses were to capecitabine monotherapy and paclitaxel. CAPOX chemotherapy was the only regimen that stood out among all other 2nd line agents with 80% success rate. Here, by success rate, we mean the rate of responses produced by one particular chemotherapy regimen. Success rates of paclitaxel and capecitabine monotherapy were 50% and 16.6%, respectively.

Overall Survival

In our study, the median overall survival of all patients who received systemic chemotherapy was 8.9 months. Systemic chemotherapy has shown significant but modest survival benefit in the management of A-GBC. Most studies have included gallbladder cancer in the fold of BTCs. Only few clinical trials were performed exclusively in patients with GBC. In these earlier trials, overall survival was around 7 months. A pooled analysis suggested differences in effectiveness of chemotherapy between gallbladder and other BTCs. Subgroup analysis showed shorter overall survival for GBC compared to cholangiocarcinoma (7.2 vs. 9.3 months). In the seminal ABC 2 trial, median overall survival was 11.7 months in the cisplatin-gemcitabine group and 8.1 months in the gemcitabine group.[8] The groupe coopérateur multidisciplinaire en oncologie study evaluated 56 patients with gallbladder and BTCs. These patients were treated with GEMOX combination. The median overall survival of patients with good PS was almost double that of patients with poor PS (15.4 months vs. 7.6 months). Gemcitabine plus carboplatin regimen produced similar result. In most studies, gemcitabine monotherapy produced a median survival of 11 months or less.

To compare the effect of various chemotherapy regimens on overall survival, we divided the chemotherapy into three groups. In our study, patients who received 1st line chemotherapy with gemcitabine and cisplatin had a median survival of 9 months, the second group of other gemcitabine doublets (gemcitabine plus oxaliplatin, gemcitabine plus carboplatin, gemcitabine plus capecitabine, and gemcitabine plus nab-paclitaxel) showed a median survival of 10 months and gemcitabine monotherapy had a median survival of 4.9 months. The difference in survival was statistically significant. When we compared gemcitabine plus platinum combination to other chemotherapy, those who received gemcitabine-platinum combination in our study had a significant improvement in overall survival of 9.9 months compared to 4.45 months in those who did not.

i. Most clinical trials include patients with PS of 0 or 1, while we included a considerable number of patients (21%) with ECOG PS of 2 or more
ii. We had a considerable number of patients (16.1%) who received monotherapy. Overall survival is low with single-agent chemotherapy even in worldwide literature
iii. Most of the clinical studies calculated survival of biliary tract cancers as a group and very few analyzed survival of gallbladder cancer separately. A pooled analysis revealed that the survival of gallbladder cancer with systemic chemotherapy is generally inferior than other biliary tract cancers like cholangiocarcinoma.[9]
    - Taking all these factors into account, we may conclude that the overall survival data generated in our study are at par with other published literature
    - Effect of demographic characteristics, patient, and tumor factors on overall survival.

BMI – we classified BMI as per the WHO/NIH criteria and tried to know if the BMI has any effect on overall

Table 1: Distribution of gallbladder stone in the study population

GB stone	Frequency	Percent
No	24	38.7
Yes	38	61.3
Total	62	100.0

Table 2: Distribution of various chemotherapy regimens in first-line setting in the study population

CT – 1ST line	Frequency	Percent
CAPE	1	1.6
GEM	9	14.5
GEM-CAPE	1	1.6
GEM-CARBO	4	6.5
GEM-CIS	35	56.5
GEM-NABPACLI	1	1.6
GEM-OX	11	17.7
Total	62	100.0

survival. The median survival in underweight patients was 4.3 months, in healthy patients 8.57 months, in overweight patients 10.0 months, and in obese patients 14.57 months. This difference was statistically significant. This shows that underweight patients have significantly poorer survival outcome than those who are not. Low BMI has a direct correlation with under and/or poor nutrition. Moreover, under or poor nutrition is associated with poorer survival. Usually, these patients have poor tolerance to chemotherapy and hence treated with suboptimal treatments in the form of single-agent chemotherapy.

Stage – theoretically, it seems that the patients who are non-metastatic should have better prognosis than those with metastatic disease because they have comparatively less advanced disease with lower disease burden. Indeed, that was the precise inference from our study too. Patients, who were non-metastatic, but could not receive curative surgery due to reasons like comorbidities, unresectability, or patient's preference, had significant survival advantage over metastatic disease (14.57 months vs. 8.5 months) [Tables 1 and 2].

CONCLUSION

The demographic characteristics obtained in our study were similar to those found in Indian and worldwide literature. Median age at presentation was 57 years. Almost three-fourth of our patients were female. Very few patients were underweight which may not be a true representation of the community scenario. Over 90% of patients had adenocarcinoma histology. Most patients received gemcitabine-based doublet chemotherapy in the first-line setting. Of them, the majority had platinum compounds, most commonly cisplatin as a partner to gemcitabine. ORR, median overall survival, and PFS to first-line chemotherapy was 53.3%, 8.9 months, and 5.33 months, respectively. Gemcitabine-based doublet especially with platinum produced the best result in this setting. Only 44% of the patients received second-line chemotherapy which included capecitabine, gemcitabine, irinotecan, or paclitaxel-based regimens. CAPOX was the most efficacious among the second-line regimens. ORR and PFS to second-line chemotherapy were 37.5% and 2.85 months, respectively. Some of the patient and disease characteristics such as low BMI, poor PS, and metastatic disease adversely affected survival.

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Original Article

Detection of Abnormal Cervical Cytology by Papanicolaou Smears at Tertiary Care Hospital - Rajkot, Gujarat, India

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Abstract

Introduction: In developing countries like India, the burden of cervical cancer is still high. According to the World Cancer statistics, >80% of all the cervical cancer cases are found in developing and low-resource countries, because of a lack of awareness. Pap test not only diagnose cervical cancers but also aids in the diagnosis of inflammatory conditions and helps in treatment.

Material and Methods: This is a retrospective study carried out at P.D.U. Medical College and Hospital, Rajkot, Gujarat during January 2021–December 2021. Total of 782 pap smears are included in the study. Both endocervix and ectocervix were sampled. Immediately slides were fixed in 95% ethyl alcohol and subsequently stained by PAP and Hand E stains. Stained slides are mounted with DPX and reported by pathologist according to Bethesda system.

Result: A total of 782 pap smears are included in the study. Out of which, 198 smears were found to have pathology accounting for 78.5%. One hundred and seventy-one smears were found to be inflammatory accounting for 21.87%. Atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, and high-grade squamous intraepithelial lesion were 0.64%, 1.28%, and 1.02%, respectively. About 0.51% cases were of squamous cell carcinoma.

Conclusion: We can conclude Pap test is a simple and cost-effective tool in the diagnosis of inflammatory, premalignant, and malignant lesions of cervix. Awareness and screening have to be done effectively which helps in detection of premalignant lesions and reduce the incidence of cervical cancer.

Key words: Bethesda system, Cervical cancer, PAP test

INTRODUCTION

In developing countries like India, the burden of cervical cancer is still high. According to the World Cancer statistics, >80% of all the cervical cancer cases are found in developing and low-resource countries, because of a lack of awareness.[1] Every year, 122,844 women in India are diagnosed with cervical cancer, and 67,477 women die from the diseases.[2] Pap test is a simple and cost-effective test. Pap smear involves collection of exfoliated cells from the cervix onto glass slides which are processed in the laboratory and examined for the presence of cervical premalignant cells. HPV is sexually transmitted oncogenenic virus and plays a key role in development of cancer.[3,4] The introduction of cytological screening by George Papanicolaou in the late 1940s was a great public health success story in cervical cancer prevention.[5] Apart from diagnosing cervical cancers pap test also aids in the diagnosis of inflammatory conditions. Cervical cancer is a preventable disease. Annual screening is recommended from the age of 25 years till three consecutive negative results before lengthening the screening interval depending n the risk group of the woman. The US Preventive Services Task Force and the American Cancer Society now recommends cytological screening every 3 years starting

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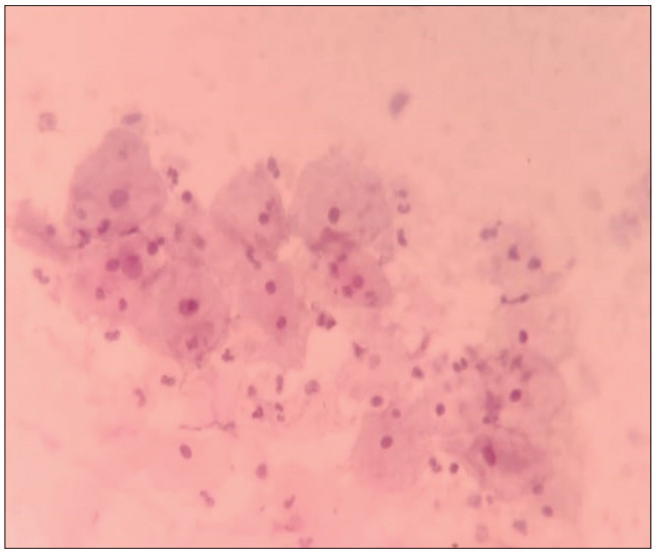

Figure 1: Clue cells in bacterial vaginosis (H and E, ×40)

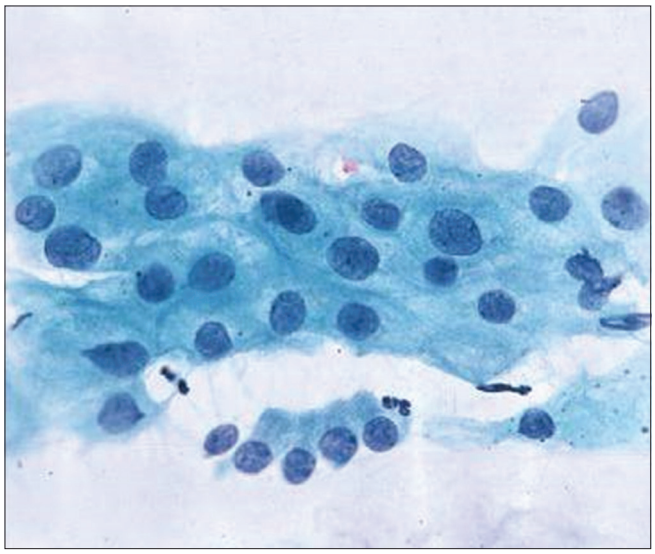

Figure 2: Atypical squamous cells of undetermined significance (pap, ×40)

from age 21 but not lower.[6,7] According to National Cancer Registry, cancers of uterine cervix and breast are leading malignancies seen in Indian women.[8] Sensitivity and specificity of pap smear screening are 50–75% and 90–99%, respectively.[9] If precancerous stages are identified early and treated it is a preventable disease.[10]

MATERIALS AND METHODS

This is a retrospective study carried out at P.D.U. Medical College and hospital, Rajkot, Gujarat during January 2021–December 2021. Total of 782 pap smears are included in the study. Smears are taken by a medical professional using modified ayers spatula which was inserted and rotated over 360 degrees. Both endocervix and ectocervix were

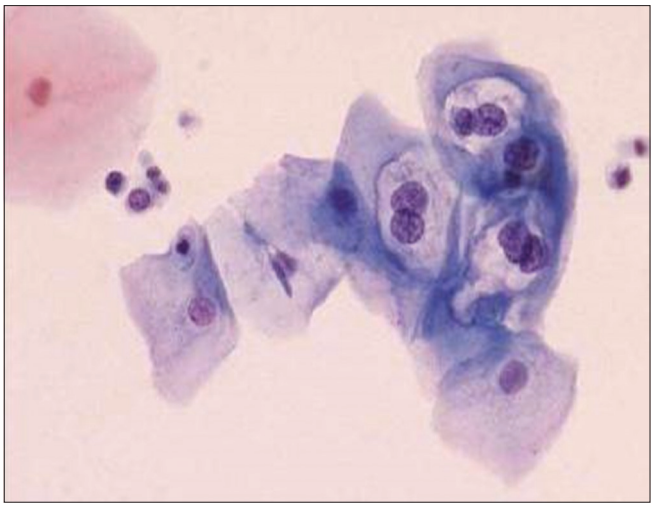

Figure 3: Low-grade squamous intraepithelial lesion (pap, ×40)

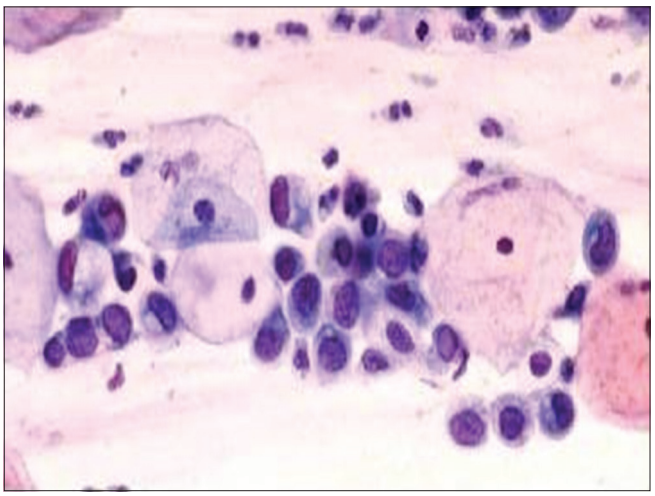

Figure 4: High-grade squamous intraepithelial lesion (pap, ×40)

sampled. Immediately slides were fixed in 95% ethyl alcohol and subsequently stained by PAP and H and E stains. PAS stain is used for fungal confirmation stained slides are mounted with DPX and reported by pathologist according to Bethesda system.

OBSERVATIONS AND RESULTS

A total of 782 pap smears are included in the study. Out of which, 80 smears were found to be unsatisfactory accounting for 10.23%. Five hundred and four smears were found to be normal on screening. Pattern of distribution of pap smear is shown in Table 1. Out of 782 pap smears, 198' smears were found to have pathology accounting for 78.5%., 171 smears were found to be inflammatory accounting for 21.87%. Atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), and high-grade squamous intraepithelial lesion (HSIL) were accounting for 0.64%,

Table 1: Number of cases according to Bethesda system

Result	Cases	Percentage
Unsatisfactory	80	10.23
NILM	504	64.45
Inflammatory	171	21.87
ASCUS	5	0.64
LSIL	10	1.28
HSIL	8	1.02
SCC	4	0.51
Total	782	100

NILM: Negative for intraepithelial lesions or malignancy, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, SCC: Squamous cell carcinoma

Table 2: Clinical presentations

Symptoms	No. of cases (N=504)
Leucorrhea	243
Low backache	309
Pain in abdomen	289
Irregular P/V bleeding	114
Itching at vulva	167
Something coming out of vagina	26
Dyspareunia	56
Dysmenorrhea	89
Burning and frequency of micturition	121

1.28%, and 1.02%, respectively. Four cases of squamous cell carcinoma were found accounting for 0.51% of total cases.

Many of the patients had more than one symptom. Among them, 243 patients had complaints of leucorrhoea, 309 low backache, and 289 pain in abdomen, 114 irregular bleeding and 56 dyspareunia as per Table 2 Abnormal pap smears are shown in Table 3. In our study, the youngest women was 22 years and the oldest women was 70 years. All the pap smears reported in the age group of 22–40 were inflammatory. ASCUS and LSIL were mostly seen in the age group of 51–60. Total eight HSIL were reported and majority are seen in age group of 51–70 years. The Most common age group of squamous cell carcinoma was 51–70 years.

DISCUSSION

The cervix is the lower part of the uterine cavity and is covered with two types of cells: The glandular and the squamous cells. The junction of these two types of cells is known as the transformation zone. Most cervical cancer originates from the transformation zone. Squamous cell carcinoma (95%) and adenocarcinoma (5%) are the two major histological types of an epithelial tumor of the cervix, but in rare cases, the tumor can also be of a non-squamous variant including adenosquamous

Table 3: Distribution of abnormal sample age-wise age group (years)

Age group (years)	NILM	Inflammatory	ASCUS	LSIL	HSIL	SCC
22–30	172	68	00	00	00	00
31–40	155	52	00	00	00	00
41–50	105	29	01	02	01	00
51–60	52	14	03	05	05	02
61–70	20	8	01	04	02	02
Total	504	171	05	10	08	04

NILM: Negative for intraepithelial lesions or malignancy, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, SCC: Squamous cell carcinoma

Table 4: Comparison of study

Result	Verma *et al.*	Divya *et al.*	Present study
NILM	19 (15.20)	160 (17.9)	504 (64.45)
Inflammatory	86 (68.80)	396 (56.4)	171 (21.27)
ASCUS	5 (4)	84 (11.95)	5 (0.64)
LSIL	7 (5.6)	00 (00)	10 (1.28)
HSIL	00 (00)	17 (2.4)	8 (1.02)
SCC	1 (0.8)	00 (00)	4 (0.51)

NILM: Negative for intraepithelial lesions or malignancy, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, SCC: Squamous cell carcinoma

carcinoma, neuroendocrine carcinoma, and glassy cell carcinoma.[11]

Screening strategies for cervical cancer include Pap smear testing alone, primary HPV testing alone, or contesting (with Pap and HPV testing). For patients under 21, screening is not required regardless of the age of initiation of sexual activity. In patients between 21 and 29, screening is initiated at age 21 with cervical cytology every 3 years. For patients aged 30–65, either Pap testing alone every 3 years or contesting (PAP and HPV testing combined) every 5 years is recommended. For patients who are above 65, the decision to continue screening depends on whether the patient has had an adequate prior screening, life expectancy, and preferences in a shared decision-making discussion. Symptomatic patients should have Pap smear testing as part of a diagnostic workup, regardless of prior screening results.[12]

Many studies have shown cervical screening by pap smear is the best technique to diagnose premalignant and malignancies of cervix. With regular follow-up and management, the incidence and mortality due to cervical cancer have reduced.

We compare our result with Verma *et al.*[13] and Divya *et al.*[14] In both study, inflammatory cases were leading while our study shows normal smear in lead.

Negative for intraepithelial lesion or malignancy category analyzed further and showed majority (91.55%) of

non-specific inflammation. There is a high incidence of Trichomonas and Candida were noted. Patients first visited them for main complaints of leucorrhoea rather than to go for specific screening in hospital. Figure 1 showing clue cells suggesting bacterial vaginosis they get easily treated with radical use of metronidazole and anti-fungal drugs.

Our study shows 0.64% cases of ASCUS, while Verma *et al.* and Divya *et al.* show 4% and 11.95%. In 2019, Guidelines allows patients with HPV + ASC-US or LSIL at their 1-year follow-up visit after colposcopic biopsy showing normal or low-grade histology to return for repeat HPV-based testing in 1 more year, rather than immediately return to colposcopy. Figure 2 showing cytomorphology of ASCUS main goal is treat women with high risk of developing invasive disease and observe women who are not at high risk of developing invasive disease and protect them from over-treatment. Our study shows eight cases of LSIL that is 1.02% while Verma *et al.* were having 5.6%. Figure 3 showing cytomorphology of LSIL observation is preferred for LSIL. Our study shows 1.02% HSIL while Divya *et al.* were having 2.4% of HSIL cases as per Table 4. Figure 4 showing cytomorphology of HSIL colposcopic biopsy is suggested according to the guidelines.

Our study shows four cases of squamous cell carcinoma that is of 0.51% while Verma *et al.* were having one case that is of 0.8%.[13,14] Cervical cancer commonly develops in women between the ages of 40–50 years and its precursor lesion usually occurs 5–10 years earlier. Therefore, it is recommended that women should have at least one Pap smear test before the age of 45 years.[15]

CONCLUSION

Pap test is a simple and cost-effective tool in the diagnosis of inflammatory, premalignant and malignant lesions of cervix. Women above the age of 30 years are recommended for regular cervical screening every year and women with epithelial abnormalities are advised for close follow-up and colposcopic biopsies. Awareness and screening programs have to be to be done effectively which helps in detection of premalignant lesions and reduce the incidence of cervical cancer.

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Original Article

A Study of Intrathecal Nalbuphine and Intrathecal Fentanyl as Adjuvants to 0.5% Hyperbaric Bupivacaine

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Abstract

Background: We want to compare the effects of intrathecal nalbuphine and intrathecal fentanyl as an adjuvant to 0.5% hyperbaric bupivacaine in cases posted for surgeries below the umbilicus.

Methods: It was a prospective, randomized, double-blind, and comparative study conducted on 60 patients undergoing elective surgeries under subarachnoid block at the Department of Anesthesiology, ACSR GMC, Nellore from June 2021 to May 2022. Sixty patients were divided into two groups Group 1 (nalbuphine) and Group 2 (fentanyl) according to adjuvant added intrathecally to 0.5% hyperbaric bupivacaine.

Results: In our study, the mean time of onset of sensory block at T10 and motor block in Group1 (nalbuphine) was earlier than Group 2 (fentanyl) and meantime for the sensory block to reach T6 in Group 1 was also earlier than Group 2 (fentanyl) with $P < 0.001$. The mean time for 2 segments regression in Group 1 was 136.784 ± 11.857 min and in Group 2 (fentanyl) was 85.983 ± 4.450 min with ($P < 0.001$) thus showing two-segments regression which is prolonged in Group 1. Duration of motor, sensory block, and time for rescue analgesia was also significantly prolonged in Group 1 (nalbuphine) compared to Group 2 (fentanyl). The adverse events in Group 1 (nalbuphine) were lesser as compared to Group 2 (fentanyl) and were statistically significant. Fall in pulse rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure was observed in both the groups following institution of spinal anesthesia.

Key words: Local anesthetic, Intrathecal adjuvants, Hyperbaric bupivacaine, Nalbuphine, Fentanyl, Visual analog scale

INTRODUCTION

Hyperbaric Bupivacaine, the local anesthetic does not have the advantage of prolonged analgesia as a single agent. Due to the early arising post-operative pain, the role of various adjuvants has been proposed and evaluated.[1]

Adjuvant drugs are pharmacological agents possessing little pharmacological effect by themselves but enhance or potentiate the action of other drugs when given at the same time. Adjuvant drugs modify LA effects and reduce side effects.

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Perioperatively these drugs affect:

- Latency, that is, time of onset of LA block
- Duration of analgesia, that is, duration of sensory and motor block
- Quality of analgesia, that is, complete and incomplete analgesia.

Postoperatively adjuvant drugs affect:

- Analgesic gap, that is, the time interval between subsequent doses administered
- Quality of analgesia, that is, patient satisfaction and care provider's impression of pain relief.

Knowledge and use of adjuvant drug therapy have rendered neuraxial analgesia more effective in the management of both acute and chronic pain conditions.[2] Among various

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adjuvants, intrathecal opioids have provided an effective prolongation of post-operative analgesia after orthopedic surgical procedures.[3,4]

Aim

The aim of this study was to study the effects of intrathecal nalbuphine and intrathecal fentanyl as adjuvants to 0.5% hyperbaric Bupivacaine in the lower abdominal and lower limb surgeries.

Objectives

The objective of this study were as follows:

a) To compare the onset and duration of sensory block.
b) To compare onset and duration of motor block.
c) To compare hemodynamic variables intraoperatively.
d) To compare adverse effects.

Source of Data

It was a prospective, randomized, double-blind, and comparative study, which was conducted on 60 patients undergoing elective lower abdominal and lower limb orthopedic surgeries under subarachnoid block at the Department of Anesthesiology, ACSR GMC, Nellore from June 2021 to May 2022. The study was conducted over 12 months.

Sample Size Calculation

$$N = 2(z\alpha+z1\text{-}\beta)^2\ s^2/d^2$$

$Z\alpha$ = 1.96 at confidence interval of 95%
$Z1\text{-}\beta$ = Power = 0.84 at 80% power
S = Standard deviation
D = Difference between 2 means.

Inclusion Criteria

The following criteria were included in the study:

- Patients aged 18–60 years
- American Society of Anesthesiologists (ASA) physical status Grades 1 and 2
- Patients undergoing elective lower abdominal and lower limb surgeries
- Patients with signed consent.

Exclusion Criteria

The following criteria were excluded from the study:

- Patients who are not willing to participate in the study.
- Patient aged below 18 and above 60 years.
- ASA physical status Grades 3 and above
- Contraindication to spinal anesthesia such as infection at the site of injection, bleeding disorders, and systemic anticoagulation.

PATIENTS AND METHODS

A total of 60 patients were randomly taken for this study and categorized into Group 1 and Group 2.

Group 1 patients received 12.5 mg of 0.5% hyperbaric bupivacaine with 1 mg Nalbuphine diluting it to 3 mL total volume and Group 2 patients received 12.5 mg of 0.5% hyperbaric bupivacaine with 25 μg Fentanyl diluting it to 3 mL total volume. After complete pre-anesthetic check-up and investigation and due consent from 60 patients of either gender, aged between 18 and 60 years, ASAs physical status Grades 1 and 2, we designed a prospective, randomized, and double-blinded study. The selected patients were randomized into two comparable groups of 30 patients each by a computer-generated random number table. Patients of Group 1 were given 12.5 mg (2.5 mL) of 0.5% hyperbaric bupivacaine with intrathecal fentanyl 25 μg, making intrathecal drug volume to 3 mL, and patients of Group 2 were given 12.5 mg (2.5 mL) of 0.5% hyperbaric bupivacaine with preservative-free intrathecal nalbuphine 1 mg, making intrathecal drug volume to 3 mL for each patient. To ensure double blindness in the study, preparation of intrathecal drugs was done by an independent anesthesiologist not involved in the study and the drug mixture was to be administered by another anesthesiologist who will be blinded and performing spinal anesthesia. None of them were further involved in the data collection of the study. Post-operative data were recorded by a post-operative resident, who was unaware of the group allocation. All enrolled patients remained fasting overnight before surgery and were premedicated with Tablet Alprazolam 0.5 mg on the night before surgery. Before the commencement of anesthesia, patients have explained the methods of sensory and motor blockade assessments. All patients have explained the visual analog scale (VAS) scoring system. After the patient was wheeled into the operation theatre, a peripheral intravenous (IV) access with an 18G IV cannula was secured and Lactated Ringer's infusion was started to replenish the overnight fasting at a rate of 10 mL/kg, standard monitoring for heart rate (HR), non-invasive blood pressure, electrocardiogram, and pulse oximetry (spO2) was commenced and recorded at 3 min intervals throughout the surgery.

Spinal anesthesia would be performed on all patients in the sitting position. Under strict aseptic precautions, using a 25G Quincke needle mid-line spinal puncture was performed at the L3–L4 level. After observing the free flow of cerebrospinal fluid, a total volume of 3 ml of spinal solution was administered to each patient over

approximately 10–15 s. Patients were moved to the supine position immediately after administering the spinal block.

Sensory and motor block characteristics were assessed in the normal lower limb at every 2 min interval until no pinprick sensation was achieved. All time intervals were calculated from the time of the end of intrathecal injection. The onset of sensory block, defined as time to reach sensory block at T10, time taken to reach sensory block at T6, time taken to achieve maximum sensory block, and time taken to two dermatome regressions of sensory analgesia were recorded.

Grading for the motor block was done according to the Bromage scale, onset of the motor block was defined as the time taken to achieve Bromage scale 3. Time taken to achieve complete motor blockade was also noted. The surgical anesthesia was considered to be achieved when the levels of sensory block reached to T6 thoracic dermatome level with the attainment of complete motor block (Bromage-3). For recovery of a block, time to two dermatome regressions and time to complete motor recoveries were recorded. The duration of effective analgesia was taken as the time from the completion of spinal injection to the time of administration of the first rescue analgesic reflected on VAS 10: 0 where 0 = No pain to 10 = Worst possible pain. Patients with VAS score ≥3 received Inj. Diclofenac sodium 75 mg intravenously for rescue analgesia. The VAS score of >3 constituted the end point of the study. Postoperatively, the sensory and motor block levels were assessed at 15 min intervals until normal sensations returned.

Hemodynamic variables in the form of systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR were noted every 5 min up to 30 min and then every 15 min up to 90 min irrespective of the duration of surgery. Hypotension (SBP < 100 mm Hg or >20% fall from the baseline value) was treated by Injection of Ephedrine 6 mg IV and an extra bolus of 100 ml of Ringer lactate. Bradycardia (HR < 50 beats/min or >20% decrease from the baseline value) was treated with Inj Atropine 0.6 mg IV. Intraoperative nausea was treated with Inj. Ondansetron 4 mg IV. Sedation was assessed by a categorical scale as used by Mostafa *et al.* and graded as 1 – Awake and alert, 2 – Awake but drowsy, responding to a verbal stimulus, 3 – Drowsy but arousable, responding to physical stimulus, and 4 – Unarousable, not responding to physical stimulus.

Statistical Analysis

Data were entered in Microsoft Excel and analyzed in SPSS software. Descriptive statistics such as mean and standard deviation were used to summarize numerical data when normally distributed and median and interquartile ranges when non-normally distributed. Categorical data were summarized as count and percentage. Chi-square test and Z-test were applied to identify the difference in success or failure rate of the two methods. Unpaired *t*-test was used to test the difference in secondary objectives. $P < 0.05$ was considered statistically significant.

OBSERVATIONS AND RESULTS

Comparison of Demographic Parameters

The below Table 1 shows that there was no significant difference in age ($P = 0.190$).

The below Table 2 shows that there was no significant difference in weight ($P = 0.060$).

The below Table 3 shows that there was no significant difference in Weight (p-value-0.654).

The below Table 4 shows that there was no significant difference in gender (p-value-0.805).

The below Table 5 shows that there was no significant difference in Age (p-value-0.190).

Inference: Both groups are comparable concerning demographic parameters.

Table 1: Comparison of age distribution

Age distribution	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Mean age in years	42.03±11.18	42.16±12.95	0.190

Table 2: Comparison of weight distribution

Weight distribution	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Mean weight in kg	59.1±6.66	58.5±6.98	0.060

Table 3: Comparison of height distribution

Height distribution	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Mean weight in centimeters	167±6.74	165.6±9.14	0.654

Table 4: Comparison of gender distribution

Gender	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Male	12	11	0.805
Female	18	19	

Comparison of Study Parameters

In the present study, the mean time of onset of sensory block at T10 in Group 1 was 1.546 ± 0.567 min and with Group 2 was 4.263 ± 0.688 min with $P \leq 0.001$ (Table 6).

This shows that the onset sensory block at T10 was earlier in Group 1 compared to Group 2 and was statistically significant.

In the present study, mean time for a complete sensory block at T6 in Group 1 was 5.483 ± 1.941 min and with Group 2 was 8.406 ± 1.378 min with $P < 0.001$ (Table 7).

This shows that the time taken for complete sensory block to reach T6 was earlier in Group 1 compared to Group 2 and was statistically significant.

In the present study, the mean time of onset of motor block in Group 1 was 1.983 ± 1.541 min and in Group 2 was 3.547 ± 0.961 min with $P < 0.001$ (Table 8).

This shows that the onset of motor block was earlier in Group 1 compared to Group 2 and was statistically significant.

In the present study, meantime for two segments regression in Group 1 was 136.784 ± 11.857 min and in Group 2 was 85.983 ± 4.450 min with ($P < 0.001$) (Table 9).

This shows that the mean time for two segments regression is prolonged in Group 1 compared to Group 2 and was statistically significant.

In the present study, the duration of motor block in Group 1 was 239.430 ± 12.377 min and in Group 2 was 179.070 ± 8.306 min with ($P < 0.001$) (Table 10).

This shows that the mean time for the duration of motor block in Group 1 is prolonged as compared to Group 2 and was statistically significant.

In the present study, the duration of sensory block in Group 1 was 409.913 ± 18.400 min and in Group 2 was 229.453 ± 6.980 min with ($P < 0.001$) (Table 11).

This shows that the mean duration of sensory block in Group 1 is prolonged as compared to Group 2 and was statistically significant.

In the present study, rescue analgesia time in Group 1 was 396.580 ± 18.004 min and in Group 2 was 221.483 ± 10.175 min with ($P < 0.001$) (Table 12).

This shows that the mean time for rescue analgesia, in Group 1, is prolonged as compared to Group 2 and was statistically significant.

Table 5: Comparison of ASA grading distribution

ASA Grades	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
ASA 1	16	18	0.19
ASA 2	14	12	

Table 6: Comparison of onset of sensory blockade at T10

Time of onset of Analgesia at T10	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Time in minutes	1.546±0.56	4.263±0.688	<0.001**

**Significant *p* value <0.001

Table 7: Comparison of time for complete sensory blockade at T6

Time of complete sensory block at T6	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Time in minutes	5.483±1.941	8.406±1.378	<0.001**

**Significant *p* value <0.001

Table 8: Comparison of onset of motor blockade

Onset of motor block (Bromage scale 3)	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Time in minutes	1.983±1.541	3.547±0.961	<0.001**

**Significant p value <0.001

Table 9: Comparison of time for two segments regression of sensory block

Two segment regression	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Time in minutes	136.784±11.857	85.983±4.450	<0.001**

**Significant p value <0.001

Table 10: Comparison of duration of motor block

Duration of motor blockade	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Time in minutes	239.430±12.377	179.070±4.8.306	<0.001**

**Significant p value <0.001

Table 11: Comparison of duration of sensory block

Duration of sensory blockade	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Time in minutes	409.913±18.400	229.453±6.980	<0.001**

**Significant p value <0.001

Table 12: Comparison of rescue analgesia time

Rescue analgesia	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Time in minutes	396.580±18.004	221.483±10.17	<0.001**

**Significant p value <0.001

In the present study, no adverse events were seen in Group 1 and nine patients experienced adverse events in Group 2 (Table 13).

This shows that the adverse events in Group 1 are lesser as compared to Group 2.

A fall in HR was observed in both the groups following institution of SAB. After SAB till 30 min, there was a fall in the pulse rate in Group 1 of 9% and in Group 2 of 10% (Table 14).

Fall in mean arterial pressure (MAP) was observed in both the groups following institution of SAB. After SAB till 30 min, there was significant fall in the MAP in Group 1 of 8% and in Group 2 of 13% (Table 15).

Table 13: Comparison of adverse events

Incidence of adverse effects	Group 1 (nalbuphine)	Group 2 (fentanyl)
Nausea	0	3
Vomiting	0	3
Shivering	0	3

Table 14: Comparison of pulse rate

Pulse rate (beats/min)	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Baseline	75.735±9.150	82.382±7.007	0.001
5 min	73.229±8.306	80.882±7.014	0.001
10 min	72.347±6.908	79.588±6.774	<0.001
15 min	71.823±6.229	78.176±6.474	<0.001
20 min	70.471±6.407	76.647±6.508	<0.001
25 min	70.265±5.853	75.853±5.919	<0.001
30 min	69.088±5.328	74.500±5.701	<0.001
45 min	68.294±5.012	72.765±5.522	0.001
60 min	67.706±5.300	70.971±5.000	0.011
75 min	68.324±5.574	69.147±4.943	0.521
90 min	67.294±5.530	67.882±4.740	0.639

Table 15: Comparison of mean blood pressure

MAP (in mmHg)	Group 1 (nalbuphine)	Group 2 (fentanyl)	*P*-value
Baseline	92.980±10.405	95.647±10.100	0.287
5 min	91.137±9.876	86.206±8.820	0.033
10 min	90.274±9.591	82.255±6.924	<0.001**
15 min	89.235±9.235	81.863±6.727	<0.001**
20 min	88.333±8.657	82.314±6.250	0.002**
25 min	87.059±8.182	83.157±5.263	0.022*
30 min	85.529±7.826	83.275±4.889	0.159
45 min	84.804±7.328	84.431±3.738	0.793
60 min	82.853±7.019	84.823±4.226	0.165
75 min	81.961±6.517	85.510±4.519	0.011*
90 min	80.275±6.141	86.000±4.136	<0.001**

MAP: Mean arterial pressure, **Significant p value <0.001

DISCUSSION

Nalbuphine has been used successfully over the last decade for the said purpose and has further widened the scope in regional anesthesia. The faster onset of action of local anesthetics, rapid establishment of both sensory and motor blockade, prolonged duration of analgesia into the post-operative period, dose-sparing action of local anesthetics, and stable cardiovascular parameters makes these agents a very effective adjuvant in regional anesthesia.

The following results were found:

The groups were comparable in age, gender, weight, height, and ASA grade.

Patients in Group 1 (nalbuphine) had earlier onset of sensory and motor block compared to Group 2 (fentanyl).

In present study, mean time of onset of sensory block at T10 in Group 1 (nalbuphine) was 1.546 ± 0.567 min and with Group 2 (fentanyl) was 4.263 ± 0.688 min with a ($P < 0.001$) (Table 16).

This shows an earlier onset of sensory block in Group 1.

Time to Complete Sensory Block at T6

Group 1 (nalbuphine) was 5.483 ± 1.941 min and with Group 2 (fentanyl) was 8.406 ± 1.378 min with a ($P < 0.001$), thus showing that time taken for sensory block to reach T6 is earlier in Group 1 compared to Group 2 (Table 17).

Time for 2 Segments Regression

In the present study, mean time for two segments regression in Group 1 (nalbuphine) was 136.784 ± 11.857 min and in

Table 16: Comparison of onset of sensory block with other studies

Onset of sensory block	Group 1 (nalbuphine)	Group 2 (fentanyl)
Gupta *et al.* (2016)[7] (*n*=68)	4.3±0.79	3.91±2.25
Present study (*n*=60)	1.546±0.56	4.263±0.688

Table 17: Comparison of time to complete sensory block with other studies

Complete sensory block at T6	Group 1 (nalbuphine)	Group 2 (fentanyl)
Mohamed *et al.* (2021)[5] (*n*=135)	4.02±0.74	3.64±0.73
Naaz *et al.* (2017)[6] (*n*=90)	9.8±4.15	8.1±3.84
Gupta *et al.* (2016)[7] (*n*=68)	7.13±3.81	7.4±2.72
Present study (*n*=60)	5.483±1.941	8.406±1.378

Group 2 (fentanyl) was 85.983 ± 4.450 min with $P < 0.001$ thus showing two segments regression which is prolonged in Group 1.

Duration of Sensory Blockade and Time to Rescue Analgesia

The duration of sensory blockade was taken as the time from the completion of spinal injection to the regression of sensory level till L4. Patients with VAS score ≥3 received diclofenac 75 mg intramuscularly for rescue analgesia. The VAS score of ≥3 constituted the end point of the study.

In present study, duration of sensory blockade in Group 1 (nalbuphine) was 409.913 ± 18.400 min and in Group 2 (fentanyl) was 229.453 ± 6.980 min with $P < 0.001$ (Table 18).

In the present study, rescue analgesia time in Group 1 (nalbuphine) was 396.580 ± 18.004 min and in Group 2 (fentanyl) was 221.483 ± 10.175 min with ($P < 0.001$) (Table 19).

This shows that the mean duration of sensory blockade and rescue analgesia time in Group 1 is prolonged as compared to Group 2 and was statistically significant.

Onset of Motor Block

In the present study, mean time of onset of motor block in Group 1 (nalbuphine) was 1.983 ± 1.541 min and in Group 2 (fentanyl) was 3.547 ± 0.961 min with ($P < 0.001$).

Mohamed *et al.*, in 2021,[5] conducted a double-blinded randomized controlled study using 135 patients who had given their consent. They were randomized into three comparable groups of groups of 45 patients each. The study showed that onset of motor blockade was earlier in Group N (nalbuphine).

Table 18: Comparison of duration of sensory block with other studies

Duration of sensory blockade	Group 1 (nalbuphine)	Group 2 (fentanyl)
Mohamed *et al.* (2021)[5] (*n*=135)	240.2±19.61	225.1±4.9
Naaz *et al.* (2017)[6] (*n*=90)	450±109.38	441±119.69
Present study (*n*=60)	409.913±18.400	229.453±6.980

Table 19: Comparison of time to rescue analgesia with other studies

Onset of sensory block	Group 1 (nalbuphine)	Group 2 (fentanyl)
Gupta *et al.* (2016)[7] (*n*=68)	318.64±21.92	278.74±29.67
Present study (*n*=60)	396.580±18.004	221.483±10.17

Duration of Motor Block

In our study, duration of motor block in Group 1 (nalbuphine) was 239.430 ± 12.377 min and in Group 2 (fentanyl) was 179.070 ± 8.306 min with ($P < 0.001$). This shows that the mean time for duration of motor block in Group 1 is prolonged as compared to Group 2 and was statistically significant.

Adverse Events

In the present study, emphasis was made on opioid-related side effects such as hypotension, bradycardia, respiratory depression, nausea, vomiting, shivering, urinary retention, and pruritus, nine patients had adverse effects in Group 2 (three had nausea, three had vomiting, and three had shivering). This shows that the adverse events in Group 1 (nalbuphine) are lesser as compared to Group 2 (fentanyl).

Hemodynamic Parameters

After spinal till 30 min, there was a fall in the pulse rate of 9% in Group 1 (nalbuphine) and 10% in Group 2 (fentanyl). This fall in HR is non-significant as the cutoff is taken as 20%. Fall in SBP was observed in both the groups following institution of spinal anesthesia. After spinal till 30 min, there was a fall in the SBP of 6% in Group 1 (Nalbuphine) and of 15% in Group 2 (fentanyl). This fall is non-significant as the cutoff is taken as 20% fall. Fall in DBP was observed in both the groups following institution of spinal anesthesia. After spinal till 30 minutes, there was a fall in the DBP of 9% in Group 1 (Nalbuphine) and of 11% in Group 2 (fentanyl). This fall is non-significant as the cutoff is taken as 20% fall. Fall in MAP was observed in both the groups following institution of spinal anesthesia. After spinal till 30 min, there was a fall in the SBP of 8% in Group 1 (nalbuphine) and of 13% in Group 2 (fentanyl). This fall is non-significant as the cutoff is taken as 20% fall.

CONCLUSION

We concluded that nalbuphine is a better adjuvant than fentanyl in spinal anesthesia as far as prolonged post-operative analgesia, stable cardiorespiratory parameters, and quality of intraoperative block, and patient comfort is concerned.

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Original Article

Comparative Study of Effects of Intrathecal Bupivacaine Plus Clonidine Versus Bupivacaine Plus Normal Saline for Hemodynamic Effects, Motor, and Sensory Blockade for Lower Abdominal Surgeries

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Abstract

Aim: The aim of this study is to compare Effects of Intrathecal Bupivacaine Plus Clonidine Versus Bupivacaine Plus Normal Saline for Hemodynamic Effects,Motor, and Sensory Blockade for Lower Abdominal Surgeries.

Methodology: A prospective, randomized,and controlled study of the effect of intrathecal inj clonidine 75 mcg with hyperbaric bupivacaine 0.5% 15 mg (3 ml) for the lower abdominal surgeries was conducted. Group (b), 30 patients received 3 ml of 0.5% hyperbaric bupivacaine 15 mg with 0.5 ml of normal saline.Group (BC), 30 patients received 3 ml of 0.5% of hyperbaric bupivacaine with 75 mcg of inj clonidine. Time of injection to onset of analgesia to T10 level was detected by pin prick method for onset of sensory block.

Results: Onset of sensory blockade was rapid in group BC. Sensory block to T10 level at 1 min in Group BC was 100% ,in Group "B" was 56%. The degree of fall of blood pressure in both the groups was similar with P = 0.203 with no statistical significance. Hence, hypotension is not a significant side effect in the present study.The fall in heart rate <50 was 5 in Group BC and 4 in Group B. P = 0.128 is not statistically significant. There was no statistically significant difference in the motor blockade. Duration of analgesia was significantly prolonged in Group BC when compared to Group "B" ,"P" < 0.05 which is statistically significant.

Conclusions: It can be concluded that intrathecal clonidine in the dose of 75 mcg in adults along with bupivacaine 0.5% heavy 3 ml, significantly decreases the onset time for sensory blockade and prolongs the duration of post-operative analgesia. It is not associated with any significant side effects and hence can be used as an effective alternative for opioids for prolonging spinal anesthesia.

Key words: Bupivacaine, Clonidine, Intrathecal, Lower abdominal surgeries, Normal saline

INTRODUCTION

Bupivacaine, amide linked local anesthetic with structural formulae 1-N butyle-piperidine; 2-Carboxylic acid 2, 6 dimethyl amide hydrochloride, is a highly lipid soluble substance. The pKa is 8.1 and pH is 3.5. It blocks nerve conduction by decreasing the entry of Na + ions during upstroke of action potential. A small percentage of given dose of Bupivacaine is excreted unchanged in urine. The remainder is metabolized in liver. The N-dealkylated metabolite, pipecolyroxylidine, is found in the urine. Bupivacaine like most local anesthetic agents is relatively free of side effects if it is administered in an appropriate dosage and in the appropriate anatomical location. Systemic toxic reactions to Bupivacaine usually only occur after unintentional intravascular injection or in excessive doses. The symptoms of Bupivacaine-induced

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CNS toxicity include tinnitus, light-headedness, confusion, circumoral numbness, metallic taste, and visual disturbance. If a sufficiently large dose of bupivacaine has been given, tonic clonic grand mal seizures may occur in some cases without premonitory signs. The initial signs of CNS excitement may be followed by generalized CNS depression, with cessation of seizure activity and respiratory arrest.

Clonidine is chemically 2[(2-6 dichlorophenyl) Imino] Imidozoline monohydrochloride. Clonidine is the only clinically available selective alpha-2 agonist with a selective ratio of 220: 1 for alpha-2 receptors. Clonidine is widely used during antihypertensive therapy and as a coanalgesic during chronic pain therapy. In addition, it has been given as adjuvant during spinal, epidural anesthesia and peripheral nerve blocks preferentially in combination with local anesthetics where clonidine amplifies and prolongs the local anesthetics effect. The analgesic effect of clonidine is more potent after neuraxial administration indicating a spinal site of action and favors neuraxial administration. Intrathecal injection of clonidine yields better analgesia accompanied by a 50% reduction in rescue morphine requirements. The clinically effective range intrathecally is 15–30 mcg dose of clonidine added to local anesthetic agent up to a maximum dose of 1 mcg/kg body weight.

MATERIALS AND METHODS

A prospective, randomized, and control study of the effect of intrathecal inj clonidine 75 mcg with hyperbaric bupivacaine 0.5% 15 mg (3 ml) for the lower abdominal surgeries was conducted at Government general Hospital, Rangaraya Medical College after approval by the hospital ethics committee. The study period was August 2021–February 2022. After written informed consent, patients between ages of 18 and 60 years of ASA grade-1 were selected and divided into two groups of 30 each. Group (B) 30 patients, received 3 ml of 0.5% hyperbaric bupivacaine 15 mg along with 0.5 ml of normal saline to make total of 3.5 ml solution.

Group (BC) 30 patients received 3 ml of 0.5% of hyperbaric bupivacaine along with 75 mcg of inj clonidine to make total 3.5 ml solution.

Inclusion Criteria

ASA Grade-1 and Age group 16–60 years of both sexes posted for elective lower abdominal operations were included in the study.

Exclusion Criteria

Local sepsis, bleeding diathesis, raised intracranial tension, comorbid condition such as Valvular heart diseases, diabetes mellitus, obesity, and pregnancy were excluded from the study.

Study Procedure

1. Written informed consent was obtained from all patients
2. Patients were premedicated on the night before surgery with tab ranitidine 150 mg and tab diazepam 10 mg
3. Before induction of spinal anesthesia, all patients received I.V infusion of Ringer lactate 1000 ml
4. Standard intraoperative monitoring was used (ECG, Pulse Oximetry, and Non-invasive blood pressure)
5. All Emergency drugs and equipment were kept ready.

Under strict aseptic precautions, lumbar puncture was performed using 25 g Quinkie Spinal needle with the patient in left lateral position in L3-L4 inter spinous space. After confirming free flow of CSF, either of the study drugs was injected into the subarachnoid space. Patients were turned supine immediately and were given supplemental oxygen and continued IV fluids.

Observations Made Were:

Time of onset of analgesia: Time of onset of injection of local anesthetic intrathecally to onset of analgesia to T10 level. Sensory Blockade was detected by pin prick method.

Total duration of analgesia: Time taken from the onset of analgesia to the point of the time where patient complained of pain at operative site requiring rescue analgesics.

Motor blockade was assessed: Onset of motor blockade, complete blockade, and complete recovery of motor blockade, as per the Bromage Score [Table 1]. Total duration of motor blockade was defined as time taken from onset of motor blockade to complete recovery from motor blockade.

Hypertension is noted when the fall of BP >20% from base level, which was counteracted by rapid fluid administration and finally intravenous inj mephenteramine as demanded by the situation. Bradycardia was noted when the heart rate was <50 beats/min which was counteracted by inj atropine 0.5 mg.

RESULTS

Of the 60 patients, 30 patients belong to Group BC were given, 3 ml of 0.5% bupivacaine with 75 mcg of clonidine

Table 1: Bromage score (page 4 of topic)

Grade I	Free movement of legs and feet	Nil
Grade II	Just able to flex knees with free movement of feet	33%
Grade III	Unable to flex knees but with free movement of feet	66%
Grade IV	Unable to move legs or feet	Complete 100%

and patients belonging to Group B were given 3 ml of 0.5% bupivacaine + 0.5 ml of normal saline.

There was no significant difference in the demographic data [Table 2 and Figure 1] as for mean age, male and female ratio, body weight, and the type and duration of surgical procedures in two groups.

All the patients were tested for level of blockade before starting the procedure till deemed adequate for surgery. No patients in either groups required conversion to general anesthesia or additional analgesics during surgery. Sensory blockade at 1 min was statistically significant. Onset was rapid in group BC. Sensory block to T10 level at 1 min in Group BC was 100% where as in Group "B" was 56% [Table 3]. Hence, this is statistically significant. The duration of analgesia is significantly prolonged in Group BC when compared to Group "B," the "*P*" < 0.05 which is statistically significant [Tables 4 and 5, Figure 2].

There was no statistically significant difference in the motor blockade.

There was no significant statistical difference at 5 min interval in both groups for motor as well as sensory blockade [Figure 3].

Hemodynamic characteristics: The fall in blood pressure of more than 20% of the pre-operative level was treated with mephentermine in both groups. In the present study, the fall of blood pressure was 8 in Group BC and 9 in Group B. The degree of fall in both groups was similar in both groups without any statistical significance. $P = 0.203$. Hence, the hypotension is not a significant side effect.

The fall in heart rate <50/min was treated with atropine. The fall in heart rate was 5 in Group BC and 4 in Group "B" [Table 6 and Figure 4].

Atropine users: patients in whom atropine was given for bradycardia.

Atropine non-users: patients in whom there was no bradycardia.

$P = 0.128$, it is statistically not significant.

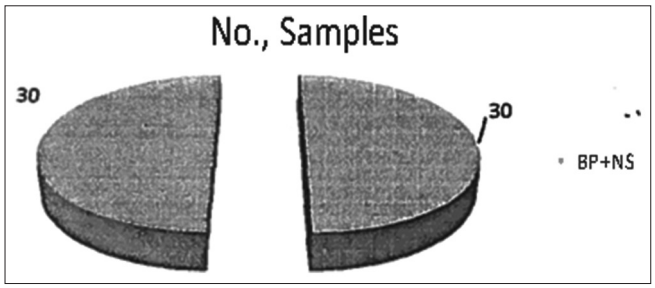

Figure 1: Demographic variables (Page 5 of Topic)

Table 2: Demographic variables (page5 of Topic)

Intervention	No. Samples
BP+NS	30
BP+CL	30
Grand total	60

Table 3: Sensory level at 1 min (page 5 of Topic)

	<T10	>T10	Total
Group BC	30	0	30
Group B	17	13	30
Total	47	13	60

DISCUSSION

Clonidine, an alpha 2 receptor agonist, is widely used during antihypertensive therapy and as a coanalgesic during chronic pain therapy. Clonidine is also used preferentially in combination with local anesthetics where it amplifies and prolongs the local anesthetics effect.

Clonidine has been demonstrated repeatedly to prolong sensory and motor block along with intrathecal local anesthetics. For example, 178 patients from five studies,[1-5] randomized to receive spinal 13.75–15 mg bupivacaine alone or with clonidine (mean dose 146 mcg, range 75–225 micro g) experienced 31% longer sensory and

Table 4: Duration of analgesia (page 5 of Topic)

	Group BC	Group B
Range	3.1–5.5 h	1.5–2.3 h
Mean	3.907 h	2.058 h
Variance	0.233	0.072
S.D	0.054	0.005

Table 5: Statistical analysis (page 5 of Topic)

	Variable 1	Variable 2
Mean	3.907	2.058333333
Variance	0.233573448	0.072772989
Observations	30	30
Pooled variance	0.153173218	
Hypothesized mean difference	O	
Df	58	
t Stat	18.29417467	
P (T≤t) one-tail	4.60439E-26	
tCritical one-tail	1.671552763	
P (T≤t) two-tail	0.0000000000	
t Critical two-tail	2.001717468	

motor block when clonidine was added (mean duration of sensory/motor block with bupivacaine alone of 2.5/2.4 h compared with 3.7/3.3 h with clonidine). Similar results are reported with addition of clonidine to smaller doses of bupivacaine.[4,6-12]

Elia *et al.*[13] added clonidine to intrathecal local anesthetics such as bupivacaine, mepivacaine, prilocaine, and tetracaine; they assessed the harmful and beneficial effects of clonidine when used as an adjuvant to intrathecal local anesthetics to surgery and concluded the study which may serve as a rational basis to help clinician whether or not to continue clonidine with intrathecal local anesthetics.

Intrathecal injection of local anesthetics reduces blood pressure primarily by reducing sympathetic outflow. Because this effect is near maximal with doses of local anesthetics causing surgical anesthesia, one would not expect greater degrees of hypotension from clonidine-induced sympatholysis when it is added to local anesthetics. Indeed, maximal decreases in blood pressure and incidence of treatment with vasoconstrictors are only slightly increased from addition of 75–225 mcg clonidine to 15 mg bupivacaine (18% decrease in blood pressure and 24% incidence of ephedrine treatment with bupivacaine alone compared with an 18% decrease in blood pressure and 35% incidence of ephedrine treatment with bupivacaine plus clonidine [n = 178]). In the present study with 15 mg bupivacaine and also with 75 mcg clonidine addition, the incidence of decrease in bp is comparable.

Table 6: Hemodynamic characteristics (page 6 of Topic)

	Patients with bradycardia	Patients without bradycardia	Total
Group BC	5	25	30
Group B	4	26	30
Total	9	51	60

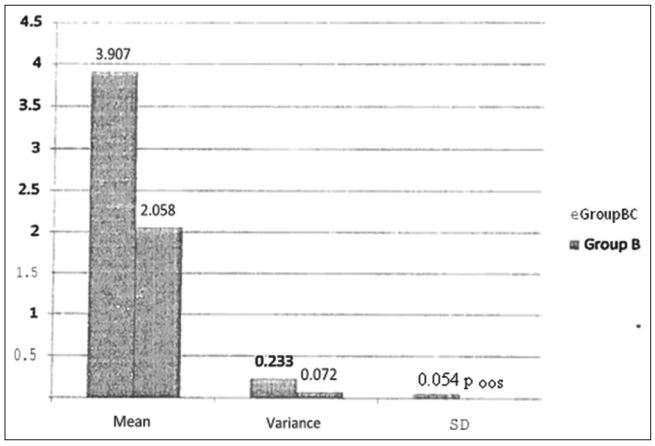

Figure 2: Duration of analgesia (Page 5 of Topic)

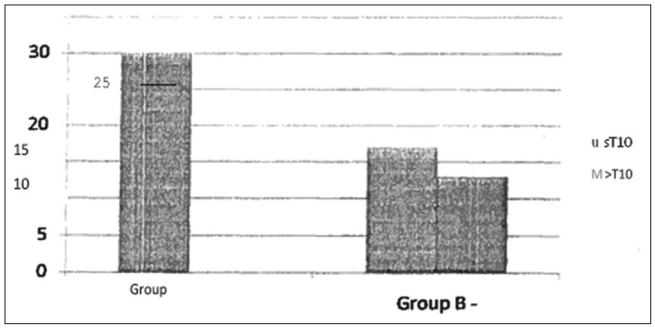

Figure 3: Sensory block at 5 min was T4–T6 in both groups (Page 5 of Topic)

Dobrydnjov *et al.*[14] tried with low dose bupivacaine 6 mg, and low dose clonidine mcg, and 30 mcg for herniorrhaphy but the results when compared with the present study, there was insufficient sensory level for five cases of hernia surgery in their study.

van Tuijl *et al.*[15] demonstrated that the addition of 75 mcg clonidine to hyperbaric bupivacaine prolongs spinal analgesia and the motor block for cesarean section and improves early analgesia but did not improve the morphine requirements in the post-operative period.

Strebel *et al.* reported that[16] clonidine prolongs spinal anesthesia.[2,4,5]

Results of the present study are in agreement with these previous studies; however, these investigators used clonidine at doses of up to 450 mcg, the present study focused on smaller doses 75 mcg).

Clonidine is used many ways; it can be used oral, intra muscular, intravenous, epidural, and intrathecal for

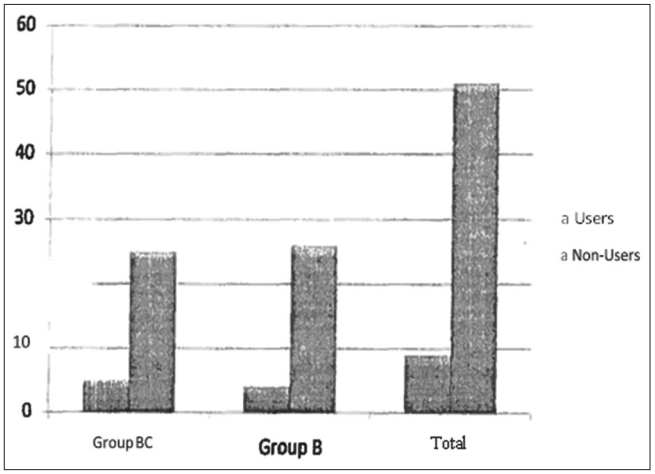

Figure 4: Atropine non users in whom there was no bradycardia (Page 6 of Topic)

obtaining the therapeutic results. However, the outcome of administration of the same drug by various routes yields different clinical results.

There were attempts to use the drug by Dobrydnjov *et al.*[17] by oral and intrathecal route for post-operative pain relief, following intrathecal Bupivacaine and they assessed the morphine requirements in the post-operative period. They concluded that addition of intrathecal clonidine prolonged analgesia and decreased morphine consumption postoperatively more than oral clonidine. Hypotension was more pronounced after oral than after intrathecal clonidine. Intrathecal clonidine is, therefore, recommended.

In clinical practice, intrathecal clonidine added to Bupivacaine is an interesting alternative to intrathecal opioids, due to a reduction of adverse effects such as respiratory depression nausea, vomiting, urinary retention, and pruritus. Further, clonidine does not potentiate opioid-induced respiratory depression, as clonidine and morphine act at different sites when mediating their analgesic effects.

Elsenach *et al.*,[18] compared the analgesic effects of intrathecal and IV clonidine with acute noxious stimulation. The data supported the value of intraspinal administration of clonidine for the treatment of acute pain and pain states associated with hyperalgesia. Analgesia from systemic administration of this drug is weak and they concluded that spinal rather than IV injection of clonidine is useful for analgesia. Hence, the present study proved the analgesic effect of intrathecal administered clonidine by prolonging the duration of analgesia of inj Bupivacaine.

Chiari *et al.*,[19] and FIIos *et al.*[20] observed the analgesic and hemodynamic effects of intrathecal clonidine as the sole analgesic agent during first stage of labor and concluded although duration and quality of analgesia were more pronounced the high incidence of hypotension limited its use and present study by supplementing the inj clonidine intrathecally along with the inj bupivacaine, balanced and offset the undue effects of inj clonidine if it was to be used alone intrathecally.

Merivirta *et al.*[21] conducted a study for unilateral analgesia after intrathecal inj bupivacaine 5 mg and intrathecal inj clonidine 15 mcg and concluded that unilateral spinal block can be achieved by combining l5 mcg of clonidine with 5 mg of hyperbaric bupivacaine. There was a small improvement in the quality of anesthesia, but, in contrast, clonidine prolonged the motor block and increased the need for vasopressors. In the present study, inj bupivacaine along with clonidine achieved sensory and motor block sufficient for the lower abdominal operations and 30% of patients required treatment for hypotension.

However, marked hemodynamic changes may limit the usefulness of intrathecal clonidine administered together with the local anesthetic, for post-operative pain relief.

The pharmacokinetic profile is consistent with rapid onset and limited distribution. Hence, 75 mcg of clonidine was selected in the present study. Intrathecal clonidine when combined with local anesthetics prolongs the sensory and motor blockade, produces analgesia for longer duration. In the present study, the analgesia achieved was for longer duration. The analgesia achieved in Group BC was 3.907 h and in Group "B" was 2.058 h. There is significant prolongation of the duration of analgesia which is beneficial, as it reduces the requirements of post-operative opioids and analgesics. Side effects with opioids are more like pruritis, respiratory depression, post-operative nausea and vomiting, constipation, and urinary retention.

Hence, there is definite advantage of clonidine which is devoid of above side effects.

It is suggested that 75 mcg clonidine may be an appropriate dose to combine with Bupivacaine as a single bolus.

CONCLUSION

From the present study, intrathecal clonidine in the dose of 75 mcg in adults along with bupivacaine 0.5% heavy 3 ml, significantly decreases the onset time for sensory blockade and prolongs the duration of post-operative analgesia. It is not associated with any significant side effects and hence can be used as an effective alternative for opioids for prolonging spinal anesthesia.

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Original Article

Seroprevalence and Associated Factors of Hepatitis-B among Antenatal Women at a Tertiary Care Hospital

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Abstract

Background: The aim was to study the seroprevalence and associated factors of Hepatitis-B among antenatal women attending the out-patient department of Obstetrics and Gynaecology, GMH, Tirupati.

Materials and Methods: This is a cross-sectional study conducted in the Department of Obstetrics and Gynaecology, GMH, Tirupati for antenatal women attending from April 2019 to March 2020.

Results: This study has found that the seroprevalence of hepatitis-B surface antigen (HBsAg) among pregnant women at Government Maternity Hospital, Tirupati was 1.2%. The socio-demographic factors and associated factors among these women were discussed in the results and are as follows: The mean age group was 25, the majority of the women were between 21 and 30 years of age, had their primary education (59%), were housewives (57%) and were parous women (78%). The high prevalence among parous women concurs with the observation that pregnant women are considered at a higher risk of hepatitis B virus infection due to increased exposure to risk factors (such as blood transfusion, intravenous drugs or surgical procedures). 3.2% of them had associated human immunodeficiency virus coinfection. 2% of women had a previous history of blood transfusions, 4.2% had a history of dental procedures, 6.3% women had a history of abortions, 5.3% women had a previous history of caesarean section and 5.3% of women had tattooing done.

Key words: Hepatitis-B surface antigen, Hepatitis B virus, Human immunodeficiency virus-Hepatitis B virus coinfection, Caesarean section, GMH

INTRODUCTION

Hepatitis B viral infection is a disease which has healthy carriers in the community. Fortunately, we can detect hepatitis B virus (HBV) infection early by testing the serum of individuals for the presence of hepatitis-B surface antigen (HBsAg). We can take the necessary steps in time to avoid further damage to the liver. Hepatitis B is a life-threatening disease and contributes to considerable human resources as well as economic loss worldwide. It is a severe and common infectious disease of the liver, affecting millions of people worldwide.[1] It is caused by a HBV which can be transmitted through percutaneous, punctures through the skin and mucosal membranes, exposure to infectious blood or blood products and body fluids.[2] Vertical transmissions of the virus from mother to child, and unsafe sexual intercourse are also essential routes for transmitting the disease. The age of acquisition of HBV is an important determinant of outcome; the earlier the age, the higher the risk of chronicity (e.g., >90% in newborns (vertical transmission), 30% in children aged 2–5 years, and <5% in adults).[3]

Viral hepatitis during pregnancy is associated with a high risk of maternal complications and a high rate of vertical transmission. Fetal and neonatal hepatitis acquired from the mother during pregnancy leads to impaired cognitive

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and physical development in the latter life of the children. The risk of vertical transmission depends on the time at which a pregnant woman acquired HBV infection and on her status of HBsAg and hepatitis B early antigen (HBeAg). In the absence of immunoprophylaxis 10–20% of women seropositive for HBsAg transmit the virus to their neonates. The vertical transmission rate reaches approximately 90% when women are seropositive for both HBsAg and HBeAg.[4]

Hepatitis-B is one of the leading causes of death globally; on the other hand, hepatocellular carcinoma (HCC) ranks fifth among humans' most frequent cancer.[5,6] As per the WHO survey, 2000 million people alive today are infected with HBV at some time in their life.

About 257 million remain infected chronically and become a carrier of the virus. Three-quarters (3/4) of the world's population lives in high endemicity areas. Every year 4 million acute clinical cases of HBV were reported and about 25% of them become carriers. One million people in a year die from chronic active hepatitis, cirrhosis of the liver or primary cancer.[1] We can quickly assess that hepatitis B is a kind of disease responsible for millions of deaths worldwide causing a public health concern. These deaths can be avoided or minimized to a great extent by creating awareness and implementing hepatitis-B vaccination among adults and especially in children. Vaccination against HBV infection can be started at birth and provides long-term protection in more than 90% of healthy people.[7]

In 1992, the WHO recommended including hepatitis-B vaccination in immunization programs of all countries. One hundred ninety-two member countries had adopted universal childhood hepatitis-B vaccination policies. This has produced a remarkable reduction in HBV-related diseases. WHO divided the regions into areas of low (<2%) prevalence, intermediate (2–8%), and high (>8%) prevalence. India has an intermediate prevalence of HBsAg, 2–10%.[8,9] with a disease burden of about 50 million. Pockets of higher endemicity are found in tribal areas where the high burden is maintained through intra-caste marriages, tribal customs, illiteracy, and poor exposure to health care resources.[3] The overall carrier rate is often quoted as 4.7% among the population's studies based on a meta-analysis.[8,10]

Limited studies are conducted so far to know the prevalence of the HBV in India. The hospital-based study cannot represent any area confined community. But the sufficient sample size may help to see the city's prevalence and may pave the way for area-specified studies. The hospital always attracts a representative sample of the whole community from near and remote areas. Sample from the hospital cannot represent a particular area of the city.

The present study aims to determine the prevalence of HBV carriers and create awareness about complications and HBV vaccinations. By knowing the prevalence, we can predict the future risk of HBV infection in the community. The preventive measures can be recommended, planned, and implemented at the appropriate place and at the proper time.

Aims and Objectives

Aim

The aim of the study was to determine the seroprevalence of HBV infection and associated factors among pregnant women attending antenatal clinic (ANC) at Government Maternity Hospital, Tirupati.

Objectives

The objectives are as follows:

1. To determine the seroprevalence of HBsAg among pregnant women attending ANC at GMH, Tirupati.
2. To determine the association of social-demographic factors and hepatitis B infection (HBsAg positivity) among pregnant women attending ANC at GMH, Tirupati.
3. To determine the association of previous blood transfusion, patient's mother, hepatitis B status, drug abuse, etc., with hepatitis B infection among HbsAg positive pregnant women attending ANC.

Inclusion Criteria

Antenatal women attending GMH, Tirupati, diagnosed HbsAg positive are included in the study.

Exclusion Criteria

Antenatal women diagnosed HbsAg positive and not willing to participate in the study.

MATERIALS AND METHODS

Place of Study

The present study is conducted at Government Maternity Hospital, Tirupati.

Study Design

The present study is a cross-sectional study. It is carried out to know the prevalence rate of HBV carriers among the patients attending Government Maternity Hospital. The study also includes knowing associated sociodemographic factors and evaluating the awareness in people about the vaccination. It creates awareness among patients and the paramedical staff.

Duration of the Study

The duration of the study is 1 year after ethical committee clearance from April 2019 to March 2020.

Sample Size

The sample size was calculated statistically taking the previous prevalence as reference. We calculated the sample size at a 5% significance level and the permissible error of 20%. The formula used for the calculation of sample size was N = 4pq/L2 (p = Present prevalence, q = 100–p, L = 20% of p). A total of 95 subjects were included in this study, which was almost equal to the calculated sample size.

Method of Collection of Data

All the antenatal women attending the antenatal clinic in Government Maternity Hospital, Tirupati, were routinely screened for HbsAg and human immunodeficiency virus (HIV). All the antenatal women who tested positive for HbsAg were informed and consent was taken for participating in the survey. After obtaining consent, a questionnaire was given to know the various sociodemographic factors involved and associated factors.

Statistical Methods

Data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS) version 16.0. The determined proportions were compared using Fisher's exact test. A $P < 0.05$ was regarded as significant.

Ethical Considerations

The study was started after the Ethical committee clearance at GMH, Tirupati.

RESULTS

This study has found that the seroprevalence of HBsAg among pregnant women at Government Maternity Hospital, Tirupati was 1.2%. The sociodemographic factors and associated factors among these women were discussed in the results and are as follows: The mean age group was 25, majority of the women between 21 to 30 years of age [Table 1]. Majority of the women had their primary education (59%) [Table 2]. Majority of the women were housewives (57%) [Table 3]. Majority of them were parous women (78%) [Table 4]. The high prevalence among parous women concurs with the observation that pregnant women are considered at a higher risk of HBV infection. The high prevalence is due to increased exposure to risk factors (such as blood transfusion, intravenous drugs, or surgical procedures) . 3.2 % of them had HIV co- infection HBV Co-infection with human immunodeficiency virus (HIV) increases the rate of transmission of viral hepatitis substantially [Table 5]. It also increases the risk for hepatotoxicity of HAART and the likelihood of an onset of an AIDS-defining illness. 2% women had the previous history of blood transfusions [Table 6], 4.2% had a history of dental procedures [Table 7], 6.3% women had abortion history [Table 8]. 1.1% of women had history of unsafe injections [Table 9], 0% of women had history of liver disease [Table 10]. 5.3 % women had the previous history of caesarean section done [Table 11], 5.3 % of women had tattooing done.

DISCUSSION

Overall seroprevalence of Hepatitis B infection in the study of antenatal women was 1.2%. This shows low endemicity of HBV according to WHO criteria . Most of the pregnant women having history of surgical procedures such as caesarean sections, instrumental deliveries, surgical evacuation for various types of abortions followed by blood transfusions.

This study has found that the seroprevalence of HBsAg among pregnant women at Government Maternity Hospital, Tirupati, was 1.2%. The sociodemographic factors and associated factors among these women were discussed in the results and are as follows: The mean age group was 25, the majority of the women between 21 and 30 years of age, majority of the women had their primary education (59%), majority of the women were housewives (57%), and majority of them were parous women (78%). The high prevalence among parous women concurs with the observation that pregnant women are considered at a higher risk of HBV infection. The high prevalence is due to increased exposure to risk factors (such as blood transfusion, intravenous drugs, or surgical procedures).

About 3.2% of them had HIV co-infection. HBV co-infection with HIV increases the rate of transmission of viral hepatitis substantially. It also increases the risk for hepatotoxicity of Highly Active Retroviral Therapy and the likelihood of an onset of an AIDS-defining illness. About 2% of women had a previous history of blood transfusions, 4.2% had a history of dental procedures, 6.3% women had abortion history, 5.3% women had a previous history of caesarean section, and 5.3% of women had tattooing done.

A similar study was conducted in 2020, in Ghana, a country in West Africa, found in one of the regions with the highest HBV prevalence.[7] This study sought to determine the seroprevalence of HBV and associated factors among pregnant women attending Korle-Bu Teaching Hospital antenatal care. The seroprevalence of HBV infection was 7.7%. As per World Health Organization's criteria for HBV severity, (≥8%; high, 2–7%; moderate and < 2%; low), the prevalence of 7.7% indicates moderate endemicity. The age group with the highest prevalence was 25–30 years. Furthermore, HBV positivity was higher among women without formal education unemployed and multiparous.

Table 1: Distribution of patients according to age

Age (years)	No. of patients	Percentage
<20	12	12.6
21–25	36	37.9
26–30	37	38.9
>30	10	10.5
Total	95	100
Mean age	25.43±4.267	

Table 2: Education distribution of patients according to education

Education	No. of patients	Percentage
Primary	59	62.1
Secondary	19	20.0
College and University	6	6.3
Non-formal	11	11.6
Total	95	100.0

Table 3: Distribution of patients according to occupation

Occupation	No. of patients	Percentage
Housewife	57	60.0
Unskilled	18	18.9
Skilled	14	14.7
Professional	6	6.3
Total	95	100.0

Table 4: Distribution of patients according to parity

Parity	No. of patients	Percentage
Nil	22	23.2
1	45	47.4
2	23	24.2
3	4	4.2
4	1	1.1
Total	95	100

Table 5: HIV co-infection

HIV seropositive	No. of patients	Percentage
Negative	92	96.8
Positive	3	3.2
Total	95	100.0

Table 6: Distribution of patients according to history of previous blood transfusions

Previous blood transfusions	No. of patients	Percentage
Negative	92	96.8
Positive	3	3.2
Total	95	100.0

Table 7: Distribution of patients according to history of dental procedures

Dental procedure	No. of patients	Percentage
Yes	4	4.2
No	91	95.8
Total	95	100.0

Table 8: Abortions

Abortions	No. of patients	Percentage
No	89	93.7
1 time	4	4.2
2 times	2	2.1
Total	95	100.0

Table 9: Unsafe injections

Unsafe Injections	No. of patients	Percentage
Yes	1	1.1
No	94	98.9
Total	95	100.0

Table 10: Liver diseases

Liver diseases	No. of patients	Percentage
Yes	0	0
No	95	100.0
Total	95	100.0

Table 11: Caesarean section

Caesarean section	No. of patients	Percentage
No	90	94.7
1 time	4	4.2
2 times	1	1.1
Total	95	100.0

Table 12: Comparison between the present study and Ghana 2020 study

S. No.	Variables	Present study	Ghana (2020)
1	Prevalence	1.2%	7.7
2	Mean age	25	25–30 years
3	Parity	Parous (78%)	Multiparous
4	Education	Primary (59%)	Illiterates
5	Occupation	Housewives (57%)	Unemployed

The main reason for the high prevalence was the lack of education. All the other factors were similar to those in our study. Educational status plays a vital role. Minimal education is necessary for the women to understand the need to register the pregnancy, follow the advice, and get the investigations done [Table 12].

An institution-based cross-sectional study was conducted among pregnant women attending antenatal clinics in the Wolaita Zone from October–November 2018.[1] A total of

Table 13: Comparison between the present study and the Wolaita zone (2018)

S. No.	Variables	Present study	Wolaita Zone
1	Prevalence	1.2%	7.3%
2	Mean age	25	26
4	Education	Primary (59%)	Diploma level (33.9%) Non-formal (18.7%)
5	Occupation	Housewives (57%)	Housewife (40.3%) Employees (29%)
6.	Blood transfusion	2%	8.4%
7	Surgical history	10.7%	10.7%
8	Dental procedures	4.2%	26%
9	Abortions	6.3%	25%

Table 14: Comparison between the present study and Antioch Turkey

S. No.	Variables	Present study	Antioch Turkey
1	Prevalence	1.2%	2.1%
2.	Blood transfusion	2%	9.51%
3.	Tattooing	5.3%	13.6%

675 women participated in the study, making a response rate of 100%. The mean age was 26 years. Four hundred forty-four (65.8%) of the respondents were urban dwellers. The majority of the study participants were housewives which accounts for 272 (40.3%), followed by employees 196 (29%) and merchants 124 (18.1%). Regarding education level, 229 (33.9%) of the women learned to the diploma level and above whereas 126 (18.7%) had no formal education. From a total of 675 study participants, 72 (10.7%) had a history of surgical procedure performed on them, 57 (8.4%) had a history of blood transfusion, 178 (26%) had a history of tooth extraction, and 492 (72.9%) had a history of genital mutilation. Among 675 participants, 48 (7.1%) had a history of multiple sexual partners, and 170 (25%) had a history of abortion. The prevalence of HBsAg among pregnant women was 49 (7.3%) [Table 13].

History of multiple sexual partners, surgical procedures, genital mutilation and tooth extraction and household or close contacts were associated with HBV. In our study at Government Maternity Hospital, Tirupati 5.3% had a history of surgical procedure performed on them, 2% had a history of blood transfusion, 4.2% had a history of tooth extraction, and 6.3% had a history of abortion. Compared with the above study, the prevalence of all the above-mentioned associated factors was less among our patients but not completely absent. We could not enquire about the history of genital mutilation and multiple sexual partners among our patients because of ethical issues. Intermediate endemicity of HBV (7.3%) was observed among mothers attending antenatal clinics in Wolaita Zone.

A similar study was conducted in Turkey.[2] The study aimed to assess the seroprevalence of HBsAg and the risk factors associated with HBV infection among pregnant women attending the University Hospital's antenatal care clinics in Antioch, Turkey. The seroprevalence of HBsAg was found to be 2.1%. History of blood transfusion, history of hepatitis, tattooing and history of household or close contacts were significantly associated with the risk of HBV infection [Table 14].

Figure 1: Our national viral hepatitis B control centre program

Figure 2: "Best Performance Award" given to the state of Andhra Pradesh given from Government of India

Sibia *et al.*, studied seroprevalence and sociodemographic factors in North India in 2016.[11] In that study, seroprevalence of HBsAg positive antenatal females was 1.11%. The mean age of HBsAg-positive pregnant women was 24.98 ± 4.16 years. Thirty-one (75.61%) subjects hailed from a rural area. 4 (09.75%) and 3 (07.31%) subjects had HBV-hepatitis

C virus (HCV) co-infection and HBV-HIV co-infection, respectively. The mean parity of women with HBV infection was 1.83 ± 0.87. The most common age group with HBV infection was 25–30 years. They concluded that the high prevalence of HBsAg seropositivity among antenatal females should call for routine vaccination against HBV infection. Our study results are similar to the above study such as mean age (25) and HIV - HbsAg co-infection (3%). Screening for HCV is not routinely done in our institution.

Bakare RA and his co-workers did a similar study in Nigeria in 2015.[6] In Nigeria, vertical transmission remains a major route of HBV infection. The seroprevalence of HBsAg was 8.3% out of which 26.7% were positive for HBeAg, 53.3% had HBeAb, 20% had neither HBeAg nor HBeAb, 100% had total HBcAb, and 86.7% had HBV DNA in their serum. The mean age was 32.1 years; the highest HBV infection rate occurred in the 25–29-year age group. Multiple sexual partners and early age at sexual debut were independent risk factors for HBV infection. The risk factors which were responsible for such high prevalence in Nigeria were not prevalent in India.

SUMMARY

For World Hepatitis Day 2020, WHO focuses on the theme "Hepatitis Free Future" to highlight the importance of addressing the prevention of mother to child transmission of HBV, launching new guidance, testing, and treatment services 2030 elimination targets.

We can integrate the hepatitis B testing and treatment of eligible pregnant women with the prevention of mother-to-child transmission of HIV and congenital syphilis with antenatal care service. This approach is often referred to as "Triple elimination" – an initiative that promotes the elimination of mother to child transmission of three infections: HIV, syphilis, and HBV.

As per the latest WHO estimates, the proportion of children under 5 years of age chronically infected with HBV dropped down to just 1% in 2019. It was around 5% in the pre-vaccine era ranging from the 1980s to the early 2000s. This drop-down marks one of the milestone targets' achievement to eliminate viral hepatitis in the Sustainable Development Goals – to reach under 1% prevalence of HBV infections in children under 5 years of age by 2020. According to the prevalence of the present study, 1.2%, our area comes under low prevalence area according to WHO. We are running National Viral Hepatitis Control Program, model centre in our institution to screen and manage the cases of Hepatitis B Viral infection [Figure 1]. Our state of Andhra Pradesh was awarded 'Best Performance State' for the National Viral Hepatitis program by the Government of India 2021 [Figure 2]. To achieve the above set goals, we need to follow the above-discussed programs and recommendations to achieve Hepatitis Free Future.

CONCLUSION

The purpose of this study is to aid clinicians in counseling their patients regarding complications, perinatal risks, and management options available to pregnant women with hepatitis B infection. We recommend the following:

1. Perform routine screening during pregnancy for HBV infection with maternal
2. HBsAg testing.
3. Administer hepatitis B vaccine and HBV immunoglobulin within 12 h of birth to all newborns of HBsAg-positive mothers, regardless of whether maternal antiviral therapy has been given during the pregnancy.
4. In pregnant women with HBV infection, we suggest HBV viral load testing in the third trimester.
5. In pregnant women with HBV infection and viral load greater than 200,000 U/ml, we should consider HBV-targeted maternal antiviral therapy to decrease the risk of intrauterine fetal infection. We suggest tenofovir as a first-line agent.
6. We recommend that women with HBV infection be encouraged to breastfeed.
7. Caesarean delivery to be performed only if indicated but not for the reduction of vertical HBV transmission

National viral hepatitis program has been launched by Ministry of health and family welfare, Government of India on the occasion of the world hepatitis day –July 28, 2018. It is an integrated initiative for the prevention and control of viral hepatitis in India. Operational guidelines for this program were:

1. To strengthen and enhance community awareness of hepatitis and lay stress on preventive measures among the general population especially high-risk groups and in hotspots.
2. Provide early diagnosis and management of viral hepatitis at all levels of healthcare
3. Develop standard diagnostic and treatment protocols for the management of viral hepatitis and its complications.
4. Strengthen the existing infrastructure facilities, build capacities of existing human resources and raise additional human resources, where required, for providing comprehensive services for the management of viral hepatitis and its complications in all districts of the country.
5. Develop linkages with the existing National programs towards awareness, prevention, diagnosis and treatment for viral hepatitis.

6. Develop a web-based "Viral Hepatitis Information and Management System" to maintain a registry of persons affected with viral hepatitis and its sequelae.[12]

Ethics Committee Approval

This journal article has been approved by the institutional ethical committee.

Informed Consent

Informed consent was obtained by participants of the present study.

Limitations

As we are carrying out our study in a tertiary care center, thinking in terms of the privacy of the patients attending antenatal OP we could not ask about the details of multiple sex partners and sexual abuse because of ethical issues. Investigations into the Hepatitis c virus are not offered in our institution.

AUTHORSHIP CONTRIBUTIONS

Dr. Vishali and Dr Nirmala Bandi - Data collection and analysis. Dr. T Bharathi and Dr K Radha - Study design and interpretation. Dr. N Lahari – Literature search. Dr. Sai Pranavi Varri - Writing, documentation.

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Original Article

Prevalence of Bacterial Vaginosis Using Amsel's Criteria In Reproductive Women attending Gynaecology OP At Government Maternity Hospital, Tirupati, Andhra Pradesh

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Abstract

Background: Vaginal discharge is the most common cause in reproductive women attending Gynaecology OP. Bacterial vaginosis is the most common cause of nonspecific vaginitis in the reproductive age group. The disease manifests as vaginal discharge with or without itching. It is associated with preterm labour, premature rupture of membranes and low birth weight in pregnancy. Early detection of the organisms and treatment is very difficult in our country due to lack of awareness and continuous follow up.

Methods: A prospective study was conducted on 300 women of reproductive age group attending Gynaecology OP at Government Maternity Hospital, Tirupati with a history of vaginal discharge over a period of one year from 2020 -2021 after obtaining approval from Institutional Ethics Committee. Diagnosis was made by history and Amsel's criteria.

Results: Among the study population, 105 (35%) participants had mucoid discharge, 60 (20%) participants had homogenous greyish white discharge, 54 (18%) participants had curdy white discharge, 54 (18%) participants had watery discharge and 27 (9%) with frothy discharge. A majority (21%) of women had Bacterial Vaginosis, followed by Candidiasis in 19%, Trichomonas vaginalis in 12%, mixed infections in 7% and no organisms in 41%.

Conclusion: Prevalence of vaginal discharge is more frequent in lower socio-economic status and rural areas. In the current study the most common cause of vaginal discharge is Bacterial Vaginosis followed by Candidiasis. Trichomonas vaginalis was the least.

Key words: Vaginal discharge, Bacterial vaginosis, Amsel's criteria

INTRODUCTION

In 1955 Herman Gardner and Dukes described foul smelling discharge in women as Non Specific Vaginitis, which is now called as Bacterial Vaginosis. It was called so because the causative agents are bacteria and there is no inflammatory response. Bacterial Vaginosis is an alteration of normal vaginal flora, that is the replacement of lactobacilli predominant vaginal flora by the other bacteria like Gardnerella Vaginalis, Mycoplasma and other Bacteroides species[1,2]. 90% of the cases are caused by Gram negative bacteria that is Gardnerella vaginalis[1]. As a result of this, pH increases and protection from overgrowth of other organisms is lost. It has been postulated that repeated alkalinisation of vagina which occurs due to frequent sexual intercourse or douching plays an important role in Bacterial Vaginosis. Prevalence of Bacterial Vaginosis is 53.1% among 21-30yrs age group and 28.1% among 31-40yrs age group. The most common cause of vaginal discharge among women of reproductive age is Bacterial Vaginosis[3]. Bacterial Vaginosis is a polymicrobial clinical syndrome resulting in the alteration of normal vaginal bacterial flora that results in the loss of H2O2 producing lactobacilli and overgrowth of other bacteria predominantly anaerobic bacteria. Anaerobic bacteria can be found in less than 1% of the flora of normal women. But in women with Bacterial Vaginosis, however

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the concentration of anaerobes and Gardnerella vaginalis and Mycoplasma hominis, is 100 to 1000 times higher than that in the normal women. Lactobacilli are usually absent[4].

Among non-pregnant women Bacterial Vaginosis is associated with pelvic inflammatory disease, Post operative cuff infections after hysterectomy, post-abortal pelvic inflammatory disease, abnormal cervical cytology, sexually transmitted infection. Risk of acquiring HIV is also increased in the presence of Bacterial Vaginosis. So, screening and early treatment of Bacterial Vaginosis is necessary before gynaecological surgery to prevent complications like pelvic inflammatory disease[5]. Recurrence and treatment failure is common unless it is diagnosed and treated. In pregnant women it is associated with complications like premature rupture of membranes, preterm birth, chorioamnionitis and post caesarean endometritis[4]. In women with Bacterial Vaginosis who are undergoing surgical abortion or hysterectomy, pre-operative treatment with metronidazole eliminates this increased risk.

In order to reduce all these complications there is a need to diagnose Bacterial Vaginosis early and start treatment. When there is high suspicion of Bacterial Vaginosis, Amsel's criteria is used as a diagnostic tool of choice. When detected and adequately treated, the cure rate can be as high as 80%, thus preventing further serious complications[6].

Amsel's Criteria

Any 3 of the following signs or symptoms are diagnostic[7].

- Homogenous thin grey-white vaginal discharge that adheres to the vaginal walls.
- Vaginal fluid pH >4.5 Positive Whiff test -On addition of 10% KOH to a drop of vaginal discharge,fishy odour occurs.
- Presence of clue cells (>20% of cells) - Clue cells - Many epithelial cells present with granular cytoplasm caused by small Gram negative bacilli adhering on their surface are called clue cells.

Clinicians who are unable to perform microscopy should use alternative diagnostic tests such as pH and amines test card, detection of Gardnerella vaginalis ribosomal RNA, or Gram stain. Specificity of Culture is very less. Therefore, culture of Gardnerella vaginalis is not recommended as a diagnostic tool[8]. We can hereby propose to use this clinical criteria for diagnosing Bacterial Vaginosis as it is rapid, economical, convenient and outpatient procedure.

OBJECTIVES

The objective of the study was to know about the prevalence of Bacterial Vaginosis among reproductive women attending Gynaecology OP with white discharge per vaginum at Government Maternity Hospital, Tirupati.

SUBJECTS AND METHODS

Study area

Government Maternity Hospital, Tirupati, Andhra Pradesh.

Study design

Prospective study

Study subjects

Reproductive women (21-40 years) attending Gynaecology OP with complaint of white discharge per vaginum.

Study duration

1 year from the date of approval from Institutional Ethical committee.

Inclusion Criteria

Non-pregnant women of reproductive age group (21-40), attending Gynaecology OPD

Exclusion Criteria

Pregnant women of reproductive age group, with associated skin diseases like lichen sclerosis, vulvar dermatoses etc.

Materials Required

- Sterile Cotton swabs
- Cusco's speculum
- Clean glass slides
- pH indicator strips
- Chemicals and reagents like normal saline, potassium hydroxide, gram staining reagents.
- Microscope

METHODS

A prospective study of 300 women of reproductive age attending gynaecology op complaining of vaginal discharge was conducted at Government Maternity Hospital, Tirupati for one year from 2020-2021 after institutional ethical committee approval. After explaining the study procedure to the patients, written and informed consent was taken from them. All identification details of patient like name, age, gender, marital status, parity and address were noted. Detailed history from patients regarding chief complaints like colour, odour, consistency of vaginal discharge, itching, dysuria, dyspareunia, lower abdominal pain, duration of complaints, drug intake, chronic illness etc were taken. Past history of having similar complaints and details of any treatment used was obtained. In menstrual history

Table 1: Sociodemographic factors

Age (Years)	Number of patients	Percentage (%)
21-25	64	21.3
26-30	106	35.3
31-35	90	30.0
36-40	40	13.3
Total	300	
Socioeconomic status		
Socioeconomic status	**Number of patients**	**Percentage (%)**
Lower (V)	132	44
Lower Middle (IV)	36	12
Middle (III)	96	32
Upper Middle (II)	27	9
Upper (I)	9	3
Total	300	100
Type of residence		
Residence	**Number of patients**	**Percentage (%)**
Rural	189	63
Urban	111	37
	300	100

Table 2: Contraceptive History

Contraceptive History	Number of patients	Percentage (%)
OCPs	12	4
Condom	15	5
IUCD	21	7
DMPA	6	2
None	246	82
Total	300	100

Table 3: Symptoms other than vaginal discharge

Symptoms	Number of Patients	Percentage (%)
Itching	128	42.7%
Foul Smell	83	27.7%
Dyspareunia	37	12.3%
Dysuria	36	12%
Lower Abdominal Pain	35	11.7%
No other symptoms	87	29%

Table 4: Types of white discharge

Type of Discharge	Number of Patients	Percentage (%)
Homogenous greyish white discharge	60	20
Curdy white discharge	54	18
Frothy discharge	27	9
Watery discharge	54	18
Mucoid discharge	105	35
Total	300	100

regularity of cycles and date of last menstrual period was noted. Treatment history regarding use of contraception, recent use of antibiotics, steroid therapy was obtained. General examination of patient was done. Patient was asked to empty the bladder and then she was made to lie in dorsal position. Cusco's speculum was gently introduced into the vagina to visualize the vagina and cervix and for the presence of abnormal discharge, cervical erosions. The colour, amount, consistency and odour of discharge were noted. After doing per speculum examination, vaginal pH was determined by using pH strips and vaginal discharge was collected with 2 cotton swabs from the posterior fornix. Out of two swabs, one was used for Saline Wet mount examination and another swab was sent to the microbiology for Gram staining. Gram staining was done to know the presence of bacteria other than lactobacilli, as a supportive evidence for clinical criteria. Whiff test was done using discharge collected on the speculum. Then bimanual examination was done for assessing uterine size, position, mobility and condition of adnexa. Final interpretation was based on Amsel's criteria as an outpatient procedure.

Table 5: Table vaginal pH

Vaginal pH	Number of patients	Percentage (%)
pH < 4.5	138	46
pH > 4.5	162	54
Total	300	100

Table 6: Whiff Test

Whiff Test	Number of patients	Percentage (%)
Positive	69	23
Negative	231	77
Total	300	100

Table 7: Amsel's Criteria

Component	Total no. of patients (N=63)	Percentage of patients
Thin homogenous greyish white discharge	51	81%
Vaginal PH >4.5	57	90.5%
Positive whiff test	47	74.6%
Clue cells+	41	65.1%

RESULTS

The present study was a prospective study conducted on 300 women of reproductive age group (21-40 years) attending gynaec opd at Government Maternity Hospital, Tirupati for one year from 2020 to2021.The following results were analysed [Table 1].

106 (35.3%) women were aged between 26-30 years, 90 (30%) participants were aged between 31-35 years ,64 (21.3%) were aged between 21-25 years, and 40 (13.3%) were aged between 36-40 years. 132 (44%) women

belonged to lower socio-economic status, 96 (32%) were from middle socio-economic status, 36 (12%) were from lower-middle socio-economic status and 27 (9%) were from upper-middle socio-economic status. 189 (63%) women were from rural areas and 111 (37%) women were from urban areas[Table 2].

246 (82%) women did not use any contraceptive method. 21 (7%) couples used Condom, 15 (5%) women had IUCD for contraception,12 (4%) women used OCPs and 6 (2%) women used DMPA injection for contraception [Table 3].

128 (42.7%) women had itching, 83(27.7%) women had foulsmell, 37 (12.3%) women had dyspareunia, 36 (12%) women had dysuria,35 (11.7%) women had lower abdominal pain, and 87 (29%) women had no other symptoms except white discharge per vaginum [Table 4].

On examination, 105 (35%) participants had mucoid discharge, 60 (20%) women had homogenous greyish white discharge, 54 (18%) women had curdy white discharge and 27 (9%) women had frothy discharge [Table 5].

162 (54%) women had vaginal pH >4.5 and 138 (46%) women had vaginal pH <4.5% [Table 6].

69 (23%) women had Whiff test positive and 231 (77%) women had Whiff test negative [Table 7].

51 (81%) women had thin homogenous greyish white discharge, 57 (90.5%) women had vaginal pH >4.5, 47 (74.6%) women had whiff test positive and in 41 (65.1%) women clue cells were detected.

DISCUSSION

Vaginal discharge is the most common presenting symptom seen in the reproductive women. One among ten females suffer from vaginal discharge in a year. The present study was a prospective study conducted on 300 women between 21-40 years attending Gynaecology OPD, Government Maternity Hospital Tirupati from 2020-2021. In the present study 106 (35.3%) patients were aged between 26-30years, followed by 90 (30%) were aged between 31-35 years, 64 (21.3%) were aged between 21-25 years and 40 (13.3%) were aged between 36-40 years. A Prospective study conducted by Basanta Kumar Pati *et al*.,[9] in 100 women of reproductive age group during the period September 2012 to September 2014, found most subjects were aged between 26-35 years. This study was similar to current study. In our study, about 44% of the study population belonged to lower socio- economic status, followed by 32% in the middle socio-economic status, 12% in the lower-middle socio-economic status, 9% in the upper-middle socio-economic status and 3% in the upper socio-economic status. Majority 63% participants were from rural areas and 37% participants were from urban areas. Contrary to study conducted in Yemen, 89.3% patients were from urban residence and 10.7% were from rural area[10].

Lack of awareness and education on hygiene leading to poor personal genital hygiene among lower socio-economic status women could be the reason significant proportion of white vaginal discharge in women belonging to lower socio- economic class.

In the current study, 7% had IUCD as the method of contraception, 5% were using condom for contraception,4% were using OCPs for contraception and 2% were using DMPA injection as a contraceptive measure. Guntoory I *et al*.,[11] conducted a study and found the least occurrence vaginal discharge in females using oral contraceptives and greater among women with permanent sterilization which is in our present study and parallel to Pant B *et al*.[12]

The most common clinical symptom in the present study was vulvar itching in 42.7%, followed by foul smelling discharge in 27.7%, dyspareunia in 12.3%, Dysuria in 12% and lower abdominal pain in 11.7%. In a study conducted by Vijayalakshmi *et al*.,[13] in between September 2009 to September 2011 revealed majority of the study subjects presenting with itching in 33.5% followed by backache in 29%, dyspareunia in 15.5%, urinary symptoms in 11%, abdominal pain in 10%, prolapse in 1% which is comparable to the present study results. Agarwal *et al*., found that majority of participants were presented with abdominal pain 48%, followed by itching in 38%, dysuria in 27.3%, dyspareunia in 18.6% and post-coital bleeding in 9.1%.

In the current study, 105 (35%) patients had mucoid discharge, 60 patients (20%) had homogenous greyish-white discharge, 54 (18%) had curdy white discharge, 27 (9%) had frothy discharge, 54 (18%) had clear watery discharge, A descriptive observational study was conducted by Masand *et al*.,[14] in 100 sexually active nonpregnant women of reproductive age group (18-45 years) between June 2012 to December 2013 at Jaipur, Rajasthan, and the results were homogenous white discharge in 52%, followed by mucopurulent in 23%, curdy white discharge in 17%, yellowish-green discharge in 8%.

In the present study, women with Bacterial Vaginosis, In 63 patients, all 4 components of Amsel's clinical criteria were present in 10 women and only 3 components were present in 53 women. Presence of any 3 components of Amsel's criteria is sufficient to diagnose Bacterial Vaginosis. In the current study prevalence of bacterial vaginosis was 21%

based on Amsel's criteria. Among women with Bacterial Vaginosis (n=63), the mean age group is 29.3 + 4.07. Majority of women 28.8% belonged to lower SES (class V), followed by upper SES (class I) 22.2%, middle SES (class III) 17.7%, lower middle SES (class IV) and upper middle SES (class II) 3.7%. Majority of women (30.6%) were from rural areas and 15.3% are from urban areas. Among women with Bacterial Vaginosis, 19.04% (12), 15.87% (10), 1.58% (1), 1.58% (1) participants had risk factors like douching, IUCD in-situ, Diabetes, Hypertension respectively and 60.31% (38) participants had no risk factors.

Sensitivity and Specificity of each component of Amsel's criteria such as homogenous grey-white discharge was 81% and 96.2%, vaginal pH > 4.5 was 90.5% and 55.7%, Clue cells on wet mount was 68.3% and 96.6%, positive whiff test were 74.6% and 90.7% respectively. According to the present study, Vaginal pH was the most sensitive and clue cells on wet mount was the most specific components of Amsel's criteria.

K Pavani, K Saileela[15] conducted a study on 204 patients of 18-45years age group with abnormal vaginal discharge at Kamineni Institute, Nalgonda. They compared the accuracy between Amsel's clinical criteria and culture with Nugent's scoring system in diagnosing Bacterial Vaginosis. According to this study sensitivity, specificity of Amsel's criteria was 78.7%, 92.9% respectively. It showed the prevalence of Bacterial Vaginosis as 24% by Amsel's criteria, 23% by Nugent scoring system and 15% by culture.

Women having symptoms other than vaginal discharge is also have significant association with Bacterial Vaginosis than women not having any other symptom apart from vaginal discharge. ($p<0.05$; significant).

Sensitivity and Specificity of each component of Amsel's criteria, homogenous grey-white discharge is 81% and 96.2%, vaginal pH > 4.5 is 90.5% and 55.7%, Clue cells on wet mount is 68.3% and 96.6%, positive whiff test are respectively. According to the present study, vaginal pH is the most sensitive and clue cells on wet mount is the most specific components of Amsel's criteria.

CONCLUSION

In the present study which included 300 women, prevalence of vaginal discharge more frequent in women belonging to low socio-economic group coming from rural areas. In the current study the most common cause of vaginal discharge was Bacterial Vaginosis followed by Candidiasis followed by Trichomonas vaginalis. Bacterial Vaginosis by Amsel's criteria is simple, quick, economical and Outpatient Day procedure. There is a need for community awareness about healthcare facilities and self-concern in women.

Limitations and Recommendations

- Smaller sample size and hospital-based study were the significant limitations of the present study. Only women with white discharge were included in the study. Asymptomatic women were not included.
- This leads to the selection bias in the study.
- Therefore, the results cannot be applied to the whole population.
- The study recommends that Amsel's criteria can be used for early diagnosis for bacterial vaginosis which may lead to many complications if left untreated.
- It recommends creating community awareness about health care facilities for this purpose.

ETHICS COMMITTEE APPROVAL

This journal article has been approved by the institutional ethical committee.

INFORMED CONSENT

Informed consent was obtained by participants of the present study.

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Original Article

A Prospective Study on Hysterosalphingography and Laproscopic Chromopertubation In Evaluation of Tubal Factors of Infertility In Tertiary Care Hospital –Tirupati

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Abstract

Background: Tubal occlusion is one of the most common cause of infertility in females. Hence evaluation of tubal factors is essential for management plan of infertility. The two most important diagnostic procedures used for evaluation of tubal patency are Hysterosalphingography (HSG) and Laproscopy.

Objectives: (1) To study the uterine and tubal findings of Hysterosalpingography in infertile women. (2) To study the findings on diagnostic laparoscopy and patency of tubes by laparoscopic chromopertubation in infertile women. (3) To compare Hysterosalpingography with Laparoscopic findings in diagnosis of tubal patency in infertile women.

Methods: A hospital based prospective study was conducted on fifty infertile women attending Gynec outpatient clinic over a period of one year from 2020 -2021.Hysterosalphingography was done within 10 days of last menstrual period on outpatient procedure. If tubal block was present, laproscopy was conducted in same or next cycle. If the tubes were patent on HSG, Laproscopy was done after three cycles if pregnancy did not occur. The findings of HSG and Laproscopy were then compared.

Results: Taking Laparoscopy as gold standard, the present study evaluated HSG as a test for tubal factor of infertility. We found sensitivity of 100%, specificity of 93.6 %, with positive predictive value 50 % and negative predictive value 0f 100 %, diagnostic accuracy of 94 % with p value <0.001.

Conclusion: HSG is considered to have a high sensitivity and specificity. HSG and laparoscopy are not alternative, but are the complementary to each other in evaluation of tubal factors in infertile women. HSG had the added advantage of evaluating the uterine factor, whereas laparoscopy is good at evaluating the peritoneal and peritubal pathology.

Key words: Hysterosalphingography, Laproscopy, Tubal patency, Infertility

INTRODUCTION

80% to 90% of couples achieve conception within one year of having regular intercourse[1]. 95% conceive by the end of 2nd year[1]. Others remain infertile by end of 2nd year. At present, 8-10% couples are infertile world wide[2]. India contributes to 25% of total infertility cases worldwide.[3] Prevalence of infertility differs one state to other in India, it is 3.7% in Himachal Pradesh, Uttar Pradesh and Maharashtra[4], 5% in Andhra Pradesh, and 15% in Kashmir. Prevalence of infertility varies in same region across tribes and caste[5].

"Infertility is defined as inability to conceive even after one year of unprotected regular intercourse"[6]. Infertility is of two types primary and secondary. Primary infertility is defined as no pregnancy in the past[7]. Secondary infertility is defined as

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history of pregnancy in past irrespective of number and type and outcome[7]. "Prevalence of primary infertility in India is between 3.9 to 16.8%as per WHO estimates"[8]

Male factors contributed to 20% of infertility cases[9]. Female factors contribute to 40% to 55% of infertility cases[9]. In 10% both are accountable, other 10% are unexplained[9]. In females tubal factors contribute to 25%- 35%[10], Ovulatory dysfunction in 30% - 40%, Uterine factors in 15%[11], Cervical in5%, and Pelvic endometriosis in 6 to 10%[12].

Main cause for tubal infertility is sexually transmitted diseases most often by Chlamydia and gonococcus causing pelvic inflammatory disease, other causes being mucosal plugs in fallopian tubes, peritubal adhesions, tubo ovarian mass, hydrosalpinx, tubal endometriosis.

Infertility in present times has become a major problem confronting gynaecologists. At present times females have become more career oriented and they are getting lately married, infertility has become a common problem causing concern to the couple. As a result, infertility and its treatment has caused a serious strain on their interpersonal relationship, and also disturbed relationships with other people[13]

Tubal blockage is one of the most frequent causes of infertility in women. The degree of tubal pathology determines the possibility for fertility. The evaluation of the fallopian tube is necessary to determine the management plan of infertility. A number of diagnostic tests are being used in clinical practice to assess tubal patency as part of the work-up for infertility.

The degree of tubal pathology determines the possibility for fertility. The evaluation of the fallopian tube is necessary to determine the management plan of infertility. A number of diagnostic tests are being used in clinical practice to assess tubal patency as part of workup for subfertility.

The most commonly used tests are hysterosalpingography (HSG) and laparoscopy. The HSG is a contrast enhanced fluoroscopic and flat plate study used to evaluate the endometrial cavity and fallopian tubes. It has been a test in the workup of infertile couples as a minimally invasive method of evaluating tubal patency and is performed as the first line approach for assessing tubal pathology[14]. Whereas laparoscopy is considered the clinical reference test for diagnosing tubal pathology. Laparoscopy allows visualization of peri-adnexal adhesions and the presence of endometriosis, which cannot be done with HSG[14].

Hysterosalpingography and diagnostic laparoscopic chromopertubation were complementary to each other because HSG studies the intraluminal pathology whereas laparoscopy offers diagnosis of peritubal and peritoneal pathology. There are not many studies in our population comparing these two modalitiies. So, this study aims to compare and correlate the HSG and Laparoscopy findings.

MATERIALS AND METHODS

A hospital based prospective study was conducted at Government Maternity hospital, Tirupati after obtaining approval from institutional Ethics Committee. The study was conducted in time period 2020-2021. 50 infertile patients both primary and secondary, attending the outpatient clinic in Government Maternity Hospital, Tirupati were selected for the study.

Inclusion Criteria

1. Women with primary or secondary infertility.
2. Age between 20 to 35 years.
3. Normal bimanual pelvic examination

Exclusion Criteria

1. Active Pelvic inflammatory disease.
2. Active Cervical or Vaginal infection.
3. Other medical or surgical disorders.
4. Suspected Genital Tuberculosis.
5. Any medical conditions that preclude laparoscopy.
6. Husband with azoospermia.
7. Active Abnormal uterine bleeding.

METHODS

- Both primary and secondary infertile cases attending the outpatient clinic in Government Maternity Hospital, Tirupati were selected for the study.
- Infertile couple were first counselled, and informed consent was taken for the study.
- Thorough history of both partners was taken followed by general examination and bimanual pelvic examination of the woman. Basic investigations like Haemoglobin, Serological tests, Semen analysis, urine analysis, thyroid profile were done. Transvaginal ultrasound was done on day3 and day 5. After initial evaluation of the couple Hysterosalpingography was done within 10 days of Last menstrual period as an outpatient procedure. If there was any infection it was treated and then Hysterosalpingography done. Patient was given two tablets of misoprostol, to be taken orally at night before the procedure. This procedure was done in X –Ray room in maternity hospital in OBG Department, Tirupati. Prior to procedure the bladder was emptied, injection Hyoscine given intramuscularly on deltoid and patient placed in dorsal

Table 1: Sociodemographic factorsfor infertility in female (Tubal factors)

1) Age (yrs)	No of Patients	Percentage (%)
20-25	9	18
25-30	26	52
30-35	15	30
Total	50	100
2) SocioEconomic Status	**No of Patients**	**Percentage(%)**
Upper Middle Class	1	2
Lower Middle Class	31	62
Upper Lower Clas	18	36
Total	50	100
3) Area Distrubution	**No of Patients**	**Total**
Rural`	13	26
Urban	37	74
Total	50	100
4) Educational Status	**No of Patients**	**Percentage(%)**
ILLITERATE	4	8
Schooling	16	32
Inter and Above	30	60
Total	50	100
5) Duration of Infertility	**No of Patients**	**Percentage(%)**
1-5	29	58
6-10	18	36
>10	03	6
Total	50	100
6) Type of Infertility	**No of Patients**	**Percentage(%)**
Primary	41	82
Secondary	09	18
Total	50	100
7) Comorbidities	**No of Patients**	**Percentage(%)**
Obesity	05	10
Hypothyrodism	09	18
Nil	36	72
Total	50	100

Table 2: Tubal findings and patency on HSG

Tubal Findings	No of Patients	Percentage(%)
Normal (B/L Patent)	44	88
B/L Cornual Block	03	06
Left Cornual Block	02	04
B/L Infundibular Block	01	02
Total	50	100

position. Internal examination done, posterior vaginal wall retracted with speculum, cervix was visualized and anterior lip was held with allis forceps, Uterocervical length was measured. Hysterosalpingographic cannula fitted with syringe containing radio opaque dye urograffin 5 ml dye diluted with 5 ml of distilled water was introduced; speculum and allis forceps were removed and two radiographic views are taken, first one shows filling of uterine cavity and second one at completion of procedure showing tubal findings which was evidenced by peritoneal spillage.

Table 3: Utrerine findings on HSG

Uterine Findings	No Of Patients	Percentage (%)
Normal	49	98
Arcuate	1	2
Total	50	100

Table 4: Uterine and ovarian findings on laproscopy

Findings	No of Patients	Percentage(%)
Normal Uterus	33	66
PCOS	16	32
Para Ovaria Cist	01	02
Total	50	100

Table 5: Tubal findings on laproscopy

Tubal Findings	No of Patients	Percentage(%)
Normal	48	96
B/L Hydrosalphinx	01	02
Tubal Adhesion	01	02
Total	50	100

Table 6: Tubal patency findings on laproscopy chromopertubation

Tubal Findings	No of Patients	Percentage(%)
B/L Patent	46	92
B/L Not Patent	03	06
B/L Patent Left Slow Patent	01	02
Total	50	100

Table 7: Correlation of patency of fallopian tubes in HSG & laproscopic chromo tubation

	Chromopertubation		Total	P-Value
	Not Patent	Patent		
HSG Tubes				
Not Patent	03	03	06	0.001
Patent	00	44	44	
Total	03	47	50	

Later in the same cycle or next cycle laparoscopy was done if there was tubal block on Hysterosalpingography. If patient showed patent tubes on Hysterosalpingography diagnostic laparoscopy with chromopertubation was done after three cycles of menstruation if the woman did not conceive. Patient was admitted a day before surgery and preoperative preparation was done. Laparoscopy was done under general anesthesia. A one cm incision was made within or just below the lower edge of the umbilicus. Through this incision the abdominal cavity was inflated with carbon dioxide gas and pneumoperitoneum being obtained. A trocar was inserted in the same region. The cannula of the trocar was left,

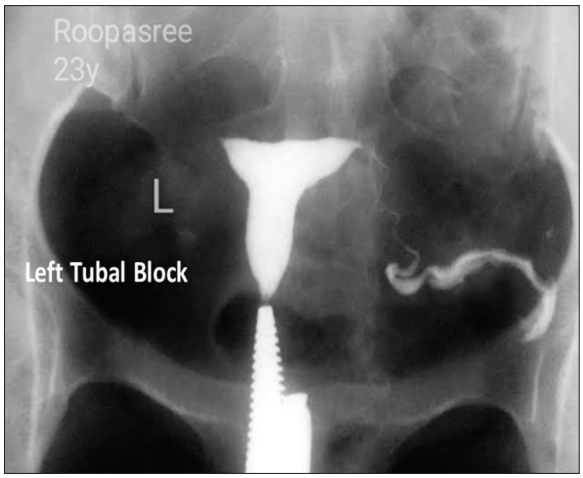

Image 1: Left tubal block on HSG

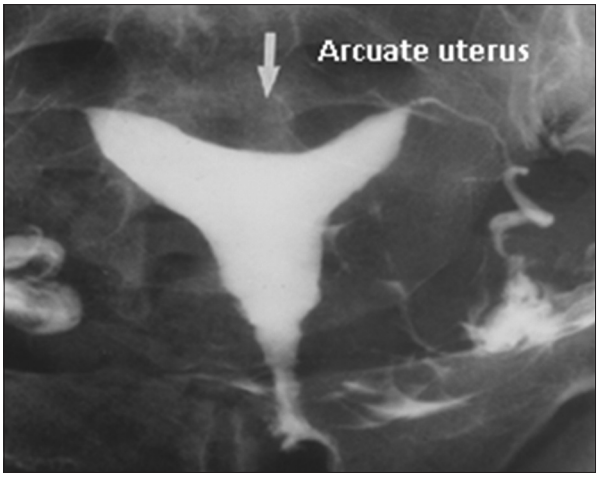

Image 2: Arcuate uterus on HSG

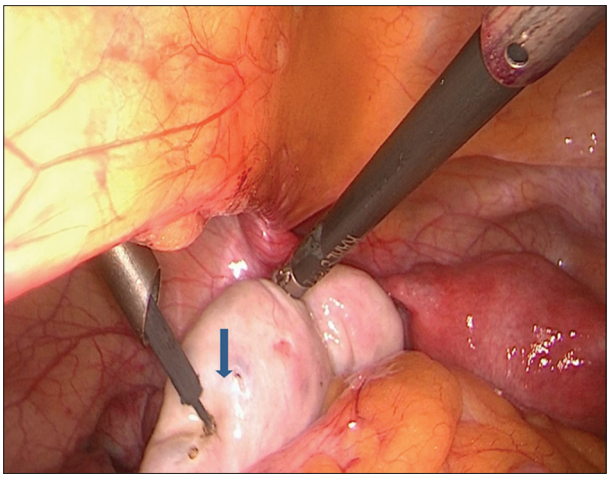

Image 3: Ovarian drilling for PCOS

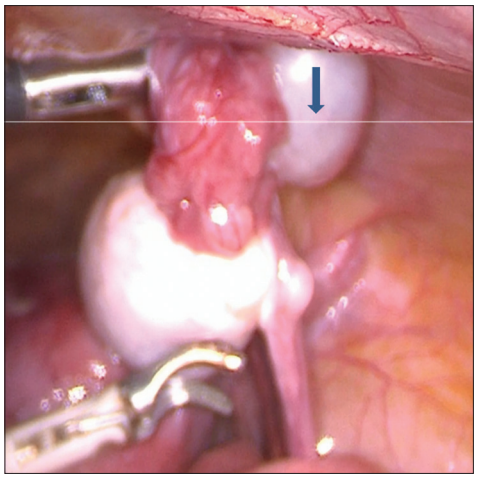

Image 4: Paraovarian cyst on laparoscopy

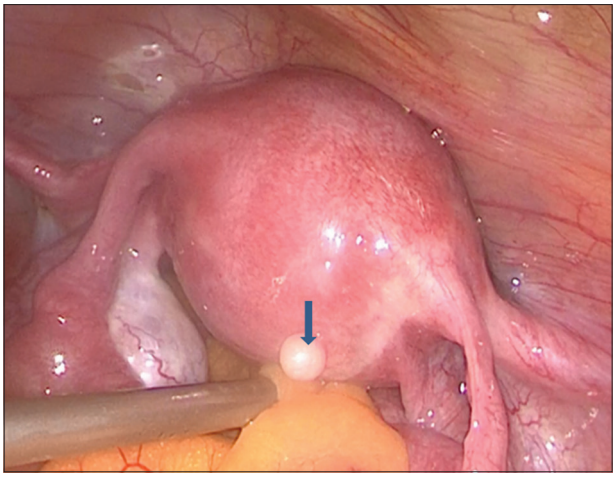

Image 5: Subserosal fibroid on laparoscopy

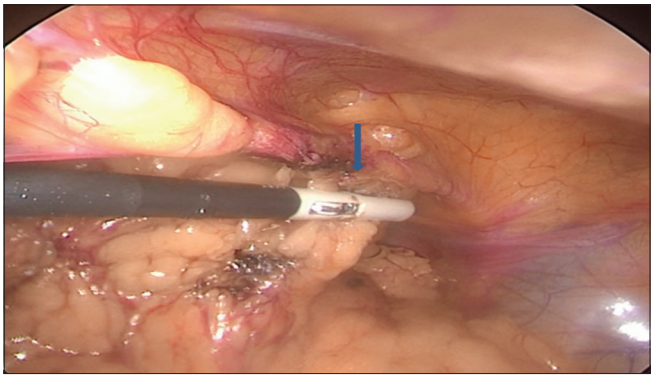

Image 6: Adhesiolysis

and the trocar was pulled out. Then a laparoscope was introduced through the cannula. The abdominal cavity and pelvic structures i.e uterus, tubes, ovaries and pouch of douglas were examined. Then by leech wilkinson cannula diluted methylene blue dye was injected into the cervix. Chromopertubation done, spill visualized in the peritoneal cavity and findings noted. The site of block, peritubal adhesions, hydrosalpinx and other pathology if any was noted. If there was Polycystic ovarian disease, ovarian drilling was done. Adhesions if present were released in same setting. Laparoscope was withdrawn after completion

of procedure. Patient was shifted to recovery room and then post-operative ward after checking the vitals. Patient was allowed to take feeds after 6 hours later. Results of Hysterosalpingography and laparoscopy were noted down. Both the findings were compared. "Results and data were analysed using MS excel software, Epi SPSS22 Version. E"

RESULTS

44 (88%) women had patent tubes with peritoneal spill [Tables 1 and 2] , 03 (6%) had b/l cornual block, 02 (4%) had left cornual block, 01 (2%) had b/l infundibular block on HSG [Table 3 and Image 1].

One Patient had Arcuate uterus on HSG

All the women had normal uterine findings on [Image 2 and Table 4] laparoscopy,one patient had subserosal fibroid and 16 patients had polycystic ovaries [Images 3-5 and Table5].

One patient had Bilateral Hydrosalpinx and one patient had peritubal adhesions on laproscopy [Image 6 and Tables 6and 7] .

Three patients showed bilateral block in both Hysterosalpingography and Laparoscopy. Another three patients had block in Hysterosalpingography but the tubes were patent in Laparoscopy. HSG correlated well with diagnostic laparoscopy, with "p value of 0.001, sensitivity of 100% and specificity of 93.6%".

DISCUSSION

Infertility has become a major problem in modern era due to late marriages and women have become more career oriented. Tubal factors are an important causes of female infertility. A prospective study was carried out on 50 infertile women in Government Maternity hospital, Tirupati,a tertiary care hospital over a period of one year from 2020 -2021. Hysterosalphingography and Laproscopic chromopertubation was done in these women and findings were correlated.

Sociodemographic factors for female infertility (Tubal factors)

In the present study 26 ((52%) of the infertile women were in the 25-29 years age group. In a central Indian cross sectional study which was community basedand conducted in 2019 majority belonged to 25-29 years of age group[15]. This is similar to another study done in Mysore, India where the mean age of infertile patients was 25. 9 years[16]. 31 (62%) infertile women in the present study were from lower middle class, according to modified kuppuswamy classification[17]. But NHFS -2 showed a higher prevalence among women belonging to low socioeconomic status when compared to medium and high Socio economic status[18].

In the present study74% of infertile women were from urban area. This is similar to the study done among infertile patients in South India where most cases were from urban area[19]. However a study done in Alexandra, Uzbekistan showed infertile women from rural areas. Another study done in 2015 in Punjab showed infertile women from rural areas[20]. This could be owing to infertile women's varying levels of awareness.

In the present study, 60 % of infertile women were well educated. A South Indian study carried out on risk factors of infertility showed that women with secondary school education and above had high prevalence of infertility[19]. A US study compared areas by number of colleges present, and identified that female graduates from college have 20% fewer children, on average, than high-school graduates.[21]

In the present study about 58% women had 1-5 years of infertility duration. This is similar to the study done in Nigeria in 2004 and 2015 with mean duration of infertility of 4.48 years[22]. One South Indian Research done in Bangalore had mean duration of infertility of 5. 9 years[23]. These studies showed that most of the women took treatment for infertility within 4-5 years of marital life.

In the present study, 41(82 %) of the infertile women had primary infertility, 9 (18%) had secondary infertility. This is similar to a 2005 study in Thailand, in which 72.03%women presented with primary infertility[24]. In a study done in Maharastra in 2018 majority of women presented with primary infertility.[25]

In the present study, 18% had Hypothyroidism and 10% were obese. This is similar to the study in Punjab where 23.9% infertile women were hypothyroid[26].A study conducted in Bangalore, India showed that 8.3% of infertile women were Obese 26.7% of women were over weight and 55% women had normal body weight which is similar to the present study[27].

In the present study, 44(88%) infertile women had B/L patent fallopian tubes,three patients(6%) had Bilateral cornual block, two patients (4%) had left cornual block, one patient (2%) had infundibular block in HSG. In a Saudi Arabian study 15% of women had bilateral tubal block and 20% with unilateral tubal block on HSG[28]. In a study conducted in Dehradun, India 39% had bilateral tubal block, 4% with unilateral tubal block on HSG[29]. In a study done in Maharashtra 7% had bilateral tubal block and 8 percent had unilateral tubal block present in HSG[30].

In present study, proximal tubal obstruction wass seen near cornual end and in one case infundibular block was noted in contrast to Nigerian study where distal obstruction was

most common[31]. In a study conducted at Ambala,Haryana proximal tubal obstruction was most common which is similar to present study. This may be due to cornual spasm inspite of giving Inj.Hyoscine.

Uterine and Ovarian findings on Laparoscopy

In the present study Laproscopy showed normal uterine findings, 32% of infertile women showed Polycystic ovarian syndrome on diagnostic laparoscopy where ovarian drilling was done on same setting and one patient had left paraovarian cyst where cystectomy was done. This is similar to the study done in Bangalore where the incidence of polycystic ovarian disease in primary infertile women is 25.7% and 13.3 % in secondary infertile women[23]. In a study conducted in Haryana, India 23% ovarian factors were detected in laparoscopy of which PCOS was the most common.

Tubal findings and Tubal patency on Laparoscopy

In the present study tubal findings were normal in almost all women except one who had peritubal adhesion and other woman had bilateral hydrosalpinx. 3 women had bilateral tubal block on Laproscopic chromopertubation. In contrast, a study in Austria, 39% had bilateral tubal occlusion in laparoscopic chromopertubation[32]. This may be due to difference in incidence of pelvic inflammatory disease and sample selection.

Correlation between HSG and Laparoscopy

In the present study, 12% women had abnormal tubal pathology in HSG. Of these 6% had bilateral tubal block in laparoscopic Chromopertubation while remaining 6% had patency in laparoscopic chromopertubation. In this study sensitivity of Hysterosalpingography was 100%, specificity of 93.6%, PPV was 50%, Negative Predictive Value was 100% and diagnostic accuracy of 94 percent with p value <0.001. In a study conducted on role of HSG and Laparoscopy in Madhya Pradesh, India, sensitivity and specificity of HSG was 93.3% and 91.1% respectively, with positive predictive value 77%, negative predictive value 97.61%[33]. In a research of 61 infertile patients conducted in Maharashtra, India, the sensitivity and specificity on HSG is 90 percent and 60 percent respectively, positive predictive value is 60 percent, and negative predictive value is 90 percent, which is similar to the current study[30]. In a study conducted in 420 patients in USA, it was said that HSG is as efficient as Laparoscopy in tubal factor evaluation[34].

CONCLUSION

HSG is a simple and cost effective diagnostic tool in evaluating tubal factors in female infertility. It has an added advantage of evaluating the uterine factor like uterine anomalies. Space occupying lesions and intrauterine adhesions.Laparoscopy is good at evaluating the pelvic pathology such as endometriosis, adhesions and ovarian cause of female inferlity in addition to tubal factors.

HSG and Laparoscopy are thus complementary to each other in evaluation of tubal factor of infertility".

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