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Case Report

Large Left Atrial Appendage Associated with IVC Type Sinus Venosus ASD – A Rare Congenital Anomaly

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Abstract

The large left atrial (LA) appendage associated with IVC Type PAPVC is a rare congenital anomaly and diagnosis in <4 year old was documented sparsely in the literature. The large LA appendage can cause serious complications such as arrhythmias, ventricular dysfunction, and stroke. A 4-year-old child with h/o recurrent respiratory tract infections and no other significant history was diagnosed as congenital acyanotic heart disease sinus venosus ASD type and was incidentally found to have a large LA appendage. Patient underwent PAPVC repair, her post-operative was uneventful and advised regular follow-up during discharge. Incidentally diagnosed large LA appendage without any symptoms or LA thrombus requires regular follow-up and further evaluation, those who are symptomatic should be treated either surgically or clipping in cath lab early.

Key words: Atrial septal defect, Inferior vena cava, Left atrial appendage

BACKGROUND

The large left atrial (LA) appendage is a rare congenital anomaly and very rarely acquired. Large LA appendage is due to dysplastic pectinate muscles of atrium,[1] usually asymptomatic until the second to the third decade of age can present with complications of arrhythmias, stroke, and ventricular dysfunction[2] if symptomatic should be either surgically resected or to be clipped.[3,4]

CASE PRESENTATION

A 3 year-old female child presented with h/o frequent respiratory tract infections, no other significant history and on examination had a murmur. Echo showed Siunus venosus ASD ivc type where right lower pulmonary vein draining into IVC and a large LA appendage around 2.86 cm, LA velocity around 1.1 m/s, no LA thrombus, lv systolic and diastolic functions, and LA volumes are normal [Figures 1 and 2]. Blood investigations and coagulation profile were normal. Pulmonary venous anamoly closure was done surgically with short cross clamp time and short cardiopulmonary bypass time and extubated with in 2 h in ICU. Her post-operative was uneventful, discharged, and advised to have regular follow-up for LA appendage changes.

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DISCUSSION

Large LA appendage associated with IVC type PAPVC, probably first ever documented in the literature. The normal LA appendage size in adults is around 1.3–1.5 cm and the normal length of LA appendage in <4 year is yet to be documented. LA appendage grows with age and a decrease in ventricular contractility leads to elevated LA pressures. A decrease in the function of appendage contractility besides dysplastic pectinate muscles leads to further dilatation of appendage and switching from

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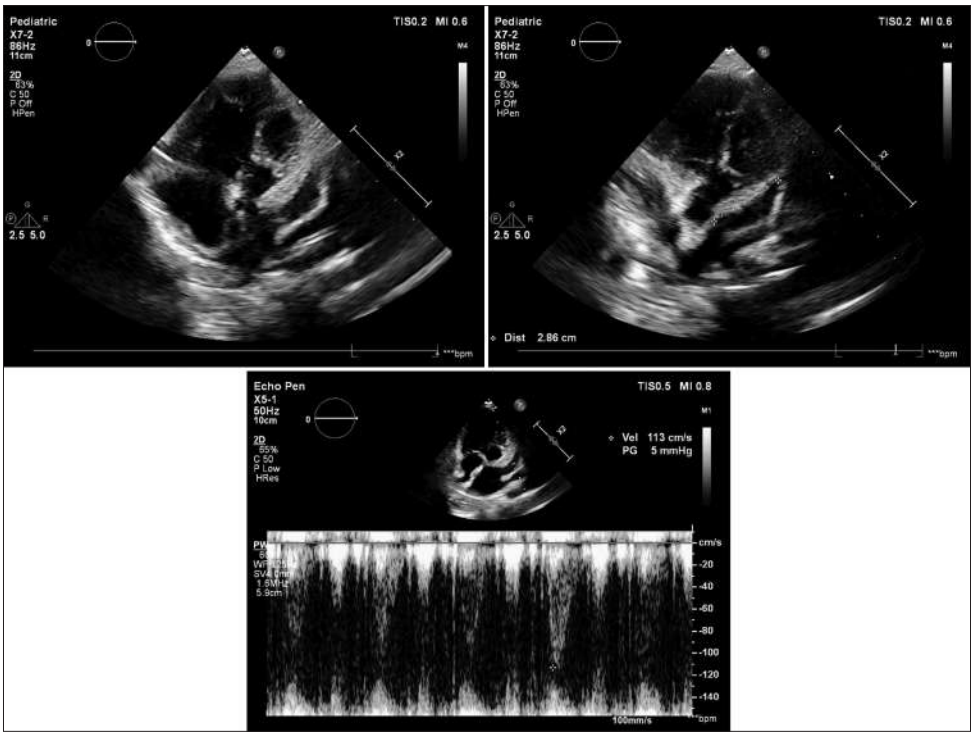

Figure 1: Transthoracic echocardiography images showing la appendage size and velocity

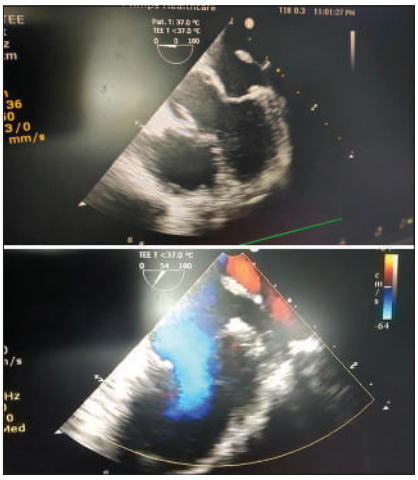

Figure 2: TEE

pump to reservoir function.[5] Enlarged LA appendage can cause complications such as arrhythmia, stroke, and ventricular dysfunction in second or third decade of age. Children can present early with the features of congestive heart failure[6] due to compression of pulmonary veins, distorted mitral annulus leading to mitral regurgitation, or symptoms of airway compression.[7] Symptomatic large LA appendage requires surgical intervention or clipping while asymptomatic patients can be managed conservatively with regular follow-up. Complications include thrombus formation and stroke in relation to the size of la appendage.[5,8] A correlation between the size of LAA and the complications such as thrombus formation and stroke has not been documented till now.

CONCLUSION

The large LA appendage in a PAPVC/IVC TYPE is a very rare anomaly probably the first to be reported in literature to the best of our knowledge. Symptomatic patients require intervention and asymptomatic patients without any thrombus can be managed conservatively with regular follow-up and further imaging of the Brain might require as there are chances of microemboli in asymptomatic patients.

REFERENCES

1. Bramlet DA, Edwards JE. Congenital aneurysm of left atrial appendage. Br Heart J 1981;45:97-100.
2. Płońska-Gościniak E, Larysz B, Jurczyk K, Kasprzak JD. Five-chambered heart: A 20-year story of left atrial appendage aneurysm. Eur Heart J 2009;30:1014.
3. Aryal MR, Hakim FA, Ghimire S, Ghimire S, Giri S, Pandit A, *et al.* Left atrial appendage aneurysm: A systematic review of 82 cases. Echocardiography 2014;31:1312-18.
4. Sharma SP, Singh D, Nakamura D, Gopinathannair R, Lakkireddy D. Incomplete endothelialization of watchmanTM device: Predictors and implications from two cases. J Atr Fibrillation 2019;11:2087.
5. Chen, Mou Y, Jiang LJ, Hu SJ. Congenital giant left atrial appendage aneurysm: A case report. J Cardiothorac Surg 2017;12:15.
6. Stone KS, Brown JW, Canal D, Caldwell R, Hurwitz R, King H. Congenital

aneurysm of the left atrial wall in Infancy. Ann Thorac Surg 1990;49: 476-8.
7. Pinede L, Loire DL. Clinical presentation of left atrial cardiac myxoma: A series of 112 consecutive cases. Medicine (Baltimore) 2001;80: 159-72.
8. Chowdhury UK, Seth S, Govindappa R, Jagia P, Malhotra P. Congenital left atrial appendage aneurysm: A case report and brief review of literature. Heart Lung Circ 2009;18:412-6.

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Case Report

Maxillary Ridge Augmentation with Chin Graft for Dental Implant Placement: A Case Report

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Abstract

In the present era, dental implants have become one of the viable treatment options to replace the lost missing teeth. Loss of teeth due to various reasons results in loss of alveolar bone, which, in turn, can hamper the ideal implant placement. Bone loss can occur in multiple dimensions, jeopardizing the foundation area for implant placement. Such cases require additional treatment steps like grafting procedures to refurbish the lost bone volume. Many grafting procedures that utilize different graft materials are available in the literature. According to various studies in literature, "Autografts have always served as gold standards." Intra oral grafts are opted due to the advantages offered by them. This case report concentrates on utilization of autogenous intraoral chin graft for restoration of the lost bone volume for ideal dental implant placement.

Key words: Chin graft, Dental implant, Maxillary ridge augmentation, Platelet rich fibrin, Sticky bone

INTRODUCTION

Morphology of residual alveolar ridge plays a key role in prosthetically driven implant treatment. This prosthetically driven concept helps in providing patients with mechanically, functionally, and esthetically satisfying treatment. Bone quantity and quality determine the long-term success of osseointegrated dental implants.[1] Bone loss can occur because of accidental trauma, long-standing edentulism, birth anomalies, periodontal infections, and diseases. As a result of this bone loss, the minimum bone dimensions required for implant placement are hampered. This necessitates bone augmentation procedure with grafting techniques before implant placement. Placement of implants in anatomically unfavorable locations results in mechanical and esthetical failure of the implants. Hence, a well-planned and staged grafting procedure can reduce the treatment failure. Numerous grafting techniques are available for rehabilitation of alveolar ridge deficiencies, which include autografts, allografts, and xenografts.[2] Autogenous grafts obtained from both extra and intraoral sites have been successfully used in reconstruction of alveolar defects. However, intraoral sites are more favored for the treatment of localized bone defects in partially edentulous jaws.[1]

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CASE REPORT

A 45-year-old female patient approached to the department of prosthodontics with chief complaint of missing tooth in the upper right front region of jaw since a year. On evaluation, it was found that the patient had lost a tooth because of a road traffic accident 1 year back. Since then, the patient has been wearing a removable prosthesis [Figure 1a]. Patient was willing for the fixed treatment alternative for the same. No gross abnormalities were detected on extra oral examination. Patient was advised for cone beam computed tomography in the region of 12. The radiograph revealed a good amount of bone height, but a definite concavity was evident on the buccal side [Figure 1b]. Patient was explained about the different treatment options possible, complexities of each, and opted for implant procedure. No relevant medical history was unveiled. Proper explanation of the sequential grafting technique and the time duration required for the entire

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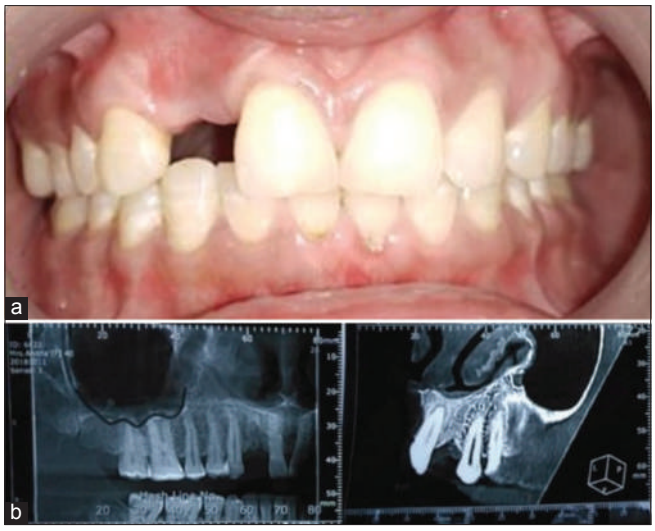

Figure 1: (a) Pre-operative intraoral (b) Pre-operative cone-beam computed tomography

treatment were given to the patient. After obtaining consent from the patient, the implant procedure was scheduled.

Treatment Protocol

Surgical procedure

Conventional surgical technique was followed for implant placement. Local anesthesia was administered to the patient. Mucoperiosteal flap was reflected in the mandibular anterior region, bone was exposed for graft from the symphysis region [Figures 2a and b]. Block dimension was marked and the bone block was sectioned [Figure 3]. Flap reflection was done at the implant placement site. Recipient site was prepared with decorticating and exposure of bone marrow for proper revascularization of bone block. Patient blood was drawn for platelet rich fibrin (PRF) preparation. The same was used for sticky bone preparation [Figures 4a and b]. Bone block was placed at the concavity site. The entire assembly was stabilized with sticky bone, PRF membrane and the suturing was done at both donor and recipient site [Figures 5a and b]. Surgical sites were covered by dressing. Medications were prescribed and post-surgical instructions were given. Recall and suture removal was done after 7 days. Patient was called again after 1 week and resin bonded temporary prosthesis was given. After 3 months, the edentulous site was re-evaluated with a radiograph. Good amount of bone healing was inferred on radiograph. Hence, it was decided to place the implant. The site was reopened, bone formation was evaluated. Bone formation was acceptable. Osteotomy preparation was done and an implant (3.3 × 11 mm) size was placed [Figure 6]. Suturing was done. Post-surgical follow-up was done after a week and temporary prosthesis was recemented. Patient was recalled after 3 months. Satisfying intraoral and radiographic healing was seen. Second stage was performed. After 2 weeks, an esthetic gingival cuff was formed. Implant level

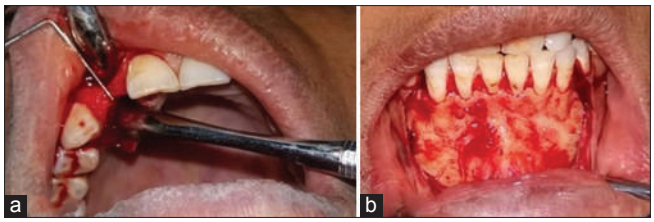

Figure 2: (a) Maxillary flap reflection and (b) Mandibular flap reflection

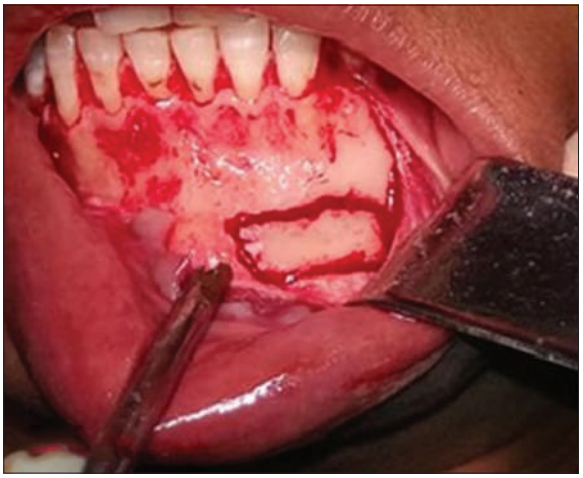

Figure 3: Graft sectioning

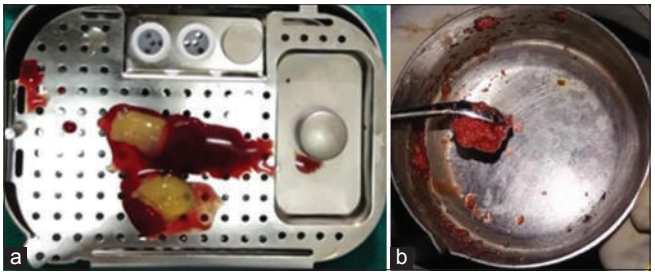

Figure 4: (a) Platelet-rich fibrin and (b) Sticky bone

impression was made and jig trial was done[Figure 7a and b]. DMLS crown was fabricated and cemented [Figure 8]. Maintenance protocol was explained to the patient. Regular follow-ups were done highlighting mast cells in epidermis in a exhausted skin block [Figures 9a and b].

DISCUSSION

Residual ridge resorption is a continuous and lifelong process. This resorption can lead to compromise in bone anatomy, laying an inappropriate foundation for implant placement. Grafting procedures have proved successful in the clinical management of human alveolar defects. Bone regeneration is a process of revascularization and substitution of the bone graft material with the host. The complex healing process between the graft material and host tissues determines the quality and quantity of new

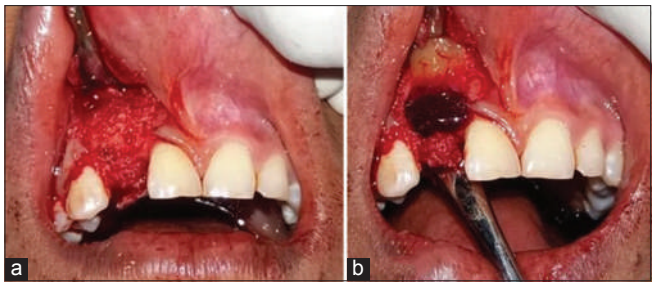

Figure 5: (a) Sticky bone placement and (b) Platelet-rich fibrin membrane placement

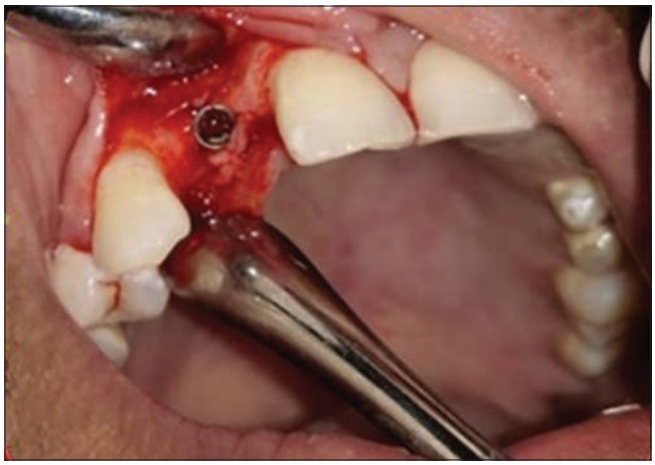

Figure 6: Implant placement

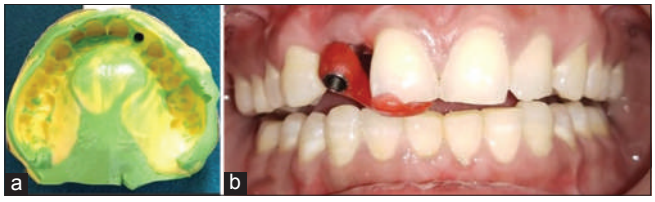

Figure 7: (a) Impression and (b) Jig trial

bone formation.[3]

Different grafting materials, such as alloplasts, allografts, autografts, and xenografts, are utilized alone or in combination with grafting techniques. The osteogenic potential of autogenous grafts, which imparts osteoinductive and osteoconductive properties, has made them the "gold standard" of grafting procedures. As these grafts have minimal chances of any immunological reactions or graft rejections, these characteristics add up to their advantages.[4] Autogenous bone graft can be obtained from extraoral or intraoral sites. Tibial metaphyses, ribs, cranium, and iliac crests are some extraoral sites. Intraoral sites include the maxillary tuberosity, mandibular ramus, and symphysis.[1]

Partially, edentulous patients rarely require extraoral autogenous bone blocks due to higher cost of treatment, ambulation, general anesthesia and the exigency for

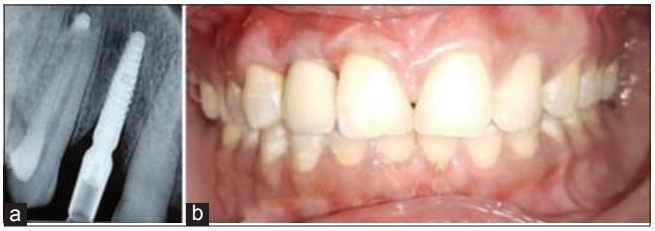

Figure 8: (a) Abutment placement and (b) Crown cementation

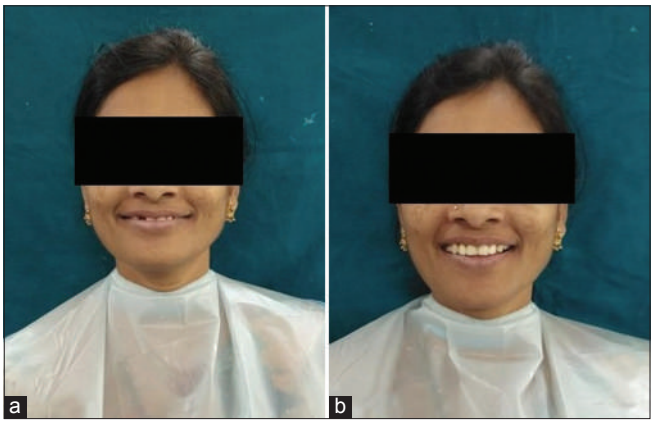

Figure 9: (a) Pre-operative extraoral (b) Post-operative extraoral

hospitalization. Extra oral grafts would rather be used in the reconstruction of larger defects. Intraoral grafting offers several assets over extraoral, because the surgical procedure can be conducted in the regular clinical set up. Intraoral grafts are good concentrates of bone morphogenetic proteins, growth factors, and have a lesser chance of resorption. Grafts from symphysis and ramus regions offer numerous advantages like accessibility; closeness of donor and recipient sites; and lesser operative time, making it an ideal option for outpatient surgery. Less morbidity, minimal discomfort, and scarring are other advantages.[3]

Mandibular bone is the best choice if the graft volume required is optimal. Clinical results have shown that mandibular block grafts are relatively safer, effective, and simpler choice for ridge augmentation in partially edentulous patients.[4] Graft volume provided by mandibular symphysis is 50% greater than the ramus, constituting of 65% of cortical and 35% of cancellous bone. This corticocancellous nature of the bone provides a faster vascularization at the recipient site, resulting in better integration and extremely favorable results. Post-surgical complications include postsurgical morbidity and flap dehiscence with or without exposure of the grafts, graft resorption, exposure, temporary, or permanent neural disturbances with the involvement of the inferior alveolar nerve and its branches, resulting in patients' unpleasant feeling. In some situations, a change in facial profile may occur.[5] None of the above complications was encountered in this case.

PRF, derivative of platelet rich plasma, can be obtained from human blood with the help of a centrifuge separator. Its applications are very common in medicine and dentistry for regenerative tissue healing procedures. Due to its adhesive hemostatic nature and healing characteristics of fibrin plasma, its use has resulted in cardiovascular, neurological, thoracic, ophthalmic, dental, and reconstructive surgeries.[6]

PRF accelerates the cicatricial process of bone tissues in dental surgeries, particularly in dental implants; providing higher potential for tissue regeneration by establishing tissue vascularization network; PRF is adept at transforming stem cells into osteoprogenitor cells; making removal of bone from another part of the body feasible for grafting procedures.[6] PRF membrane acts as "biological connector" and matrix between different components of graft material promotes soft-tissue healing; protects the surgical site; and facilitates neo-angiogenesis, and migration of osteogenic cells to the healing site.[7] Sticky bone has its own mass, can be easily shaped, and provides good handling properties. PRF membrane, enriched source of growth factor, imparts positive effect when used as a barrier membrane over the sticky bone by enhancing new bone formation.[8]

A 4–6 months of healing time period are required for any autogenous graft before dental implant placement. Because of the greater predictability and success rate, this staged approach of graft placement has become one of the most followed techniques.[3] Minimal resorption and no additional requirement of an overlying grafting membrane unless the dimensions of the graft are inadequate and are definite advantages of grafting procedures. Block grafts require longer time for integration than cancellous bone grafts. When a block graft is used, a staged surgical approach is advocated as opposed to placing the implants with the graft.[2]

CONCLUSION

Successful implant integration requires a good foundation of bone to meet the esthetical and functional demands. Not every patient presents with an ideal bone condition. In such scenarios, different grafting techniques and materials can be utilized to enhance implant success. Staged grafting procedure for implant placement is a well-known technique in the literature with good success rate. Furthermore, the use of PRF and sticky bone increases the success rate. Proper evaluation, planning of the case, and thorough knowledge of the available materials can be utilized in the management of the compromised cases.

REFERENCES

1. Aby J, Salim PS, Sunny NA. Ridge augmentation using mandibular symphyseal bone graft for the placement of dental implant-a case report. World J Pharm Med Res (WJPMR) 2020;6:97-102.
2. Harshakumar K, Varghese NM, Ravichandran R, Lylajam S: Alveolar ridge augmentation using autogenous block bone grafts harvested from mandibular ramus to facilitate implant placement: A case report. Int J Sci Stud 2014;2:46-50.
3. Rao KV, Pagadala S. Localized ridge augmentation using autogenous block bone graft followed by dental implant placement. J Orofac Sci 2012;4:148-52.
4. Khoshha S, Hedayatipanah M, Vafaee F, Torabi S. Mandibular anterior ridge augmentation using chin graft: A clinical report. Int J Med Res Prof 2016;2:154-7.
5. Maiorana C, Ferrario S, Poli PP, Manfredini M. Autogenous chin block grafts in the aesthetic zone: A 20-year follow-up case report. Case Rep Dent 2020;2020:6525797.
6. Magalhães VS, Ribeiro RA, do Amaral JM, Pimentel AC, Paulim LA, Roman-Torres CV. The use platelet rich fibrin in dental implants: A literature review. Trends Transplant 2018;11:1-3.
7. Simonpieri A, Del Corso M, Sammartino G, Ehrenfest DM. The relevance of Choukroun's platelet-rich fibrin and metronidazole during complex maxillary rehabilitations using bone allograft. Part II: Implant surgery, prosthodontics, and survival. Implant Dent 2009;18:220-9.
8. Soni R, Priya A, Yadav H, Mishra N, Kumar L. Bone augmentation with sticky bone and platelet-rich fibrin by ridge-split technique and nasal floor engagement for immediate loading of dental implant after extracting impacted canine. Natl J Maxillofac Surg 2019;10:98-101.

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Case Report

Zinner Syndrome – A Case Report

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Abstract

Zinner syndrome is a rare congenital malformation with the distal Wolffian duct anomaly in males. The triad of unilateral renal agenesis, ipsilateral seminal vesicle cyst, and ipsilateral ejaculatory duct obstruction characterizes it. Clinically, patients present with non-specific symptoms such as dysuria, ejaculatory disorders, and hypogastric or perineal pain. The diagnostic modalities include imaging techniques such as ultrasound scans, computed tomography, and magnetic resonance imaging (MRI). However, MRI is the standard gold technique for the confirmation of diagnosis. Herein, we present the case of a 14-year-old male patient who complained of vague lower abdominal pain and dysuria. Initially, an abdominal ultrasound revealed an absent right kidney and an ipsilateral seminal cyst. However, further MRI confirmed the diagnosis.

Keywords: Zinner syndrome, Renal agenesis, Dysuria, Ejaculatory disorders, Case report, Urogenital anomaly

INTRODUCTION

Zinner syndrome is a rare congenital condition characterized by a typical triad of seminal vesicle cyst, ipsilateral renal agenesis, and ejaculatory duct obstruction.[1] Conventionally, patients present in the second or third decade of life. Infertility is one of the most serious compliations.[2] Symptoms tend to manifest with the beginning of sexual activity due to the accumulation of seminal fluid in the seminal vesicles.[3] Clinically, patients present with nonspecific symptoms such as epididymitis, perineal discomfort, abdominal pain, frequent dysuria, infertility, and seminal vesical abscess so that the diagnosis may be delayed or missed until the beginning of sexual activity.[4] Zinner syndrome can sometimes be associated with other tumours or anomalies. Various radiological investigations, including ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI), help in aiding the diagnosis, but MRI is the investigation of choice for complete imaging of the anatomy. Most cases need surgical intervention, but a few can be treated conservatively.

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CASE REPORT

A 14-year-old male patient complained of vague lower abdominal pain and dysuria. On general examination, the vitals were found to be stable, and no significant abnormality was found on the systemic examination. The appearance of external genitalia was normal. Blood picture and urine examination were within normal limits. The patient was referred to the radiology department for further management. The abdominal ultrasound revealed an absent right kidney and an ipsilateral seminal cyst. For further clarification, an MRI of the whole abdomen was preferred over a CT scan to avoid exposure to excessive radiation to the paediatric patient. MRI abdomen revealed an absent right kidney (Figure 1) and a cystic lesion at the right posterolateral aspect of the urinary bladder. A fluid debris level was noted within the cystic lesion, which was suggestive of the seminal vesical cyst (Figure 2). There was compression on the adjacent urinary bladder. The right seminal vesicle was over-distended. The right ureter was moderately dilated with the upper blind end (Figure 3). The right ejaculatory duct was found to be obstructed by a seminal cyst from above. The right ureter appeared to drain into the right ejaculatory duct (Figure 4).

DISCUSSION

Zinner syndrome is a rare congenital malformation with the distal Wolffian duct anomaly in males, characterized by

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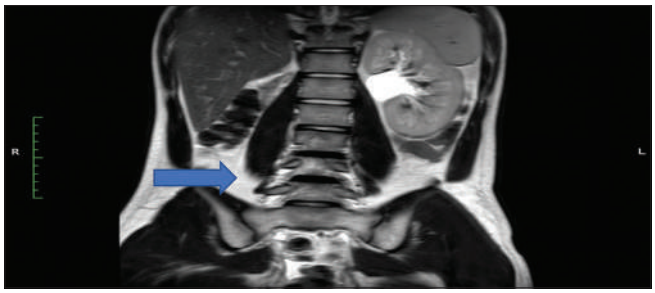

Figure 1: T2-weighted coronal section image showing absent right kidney

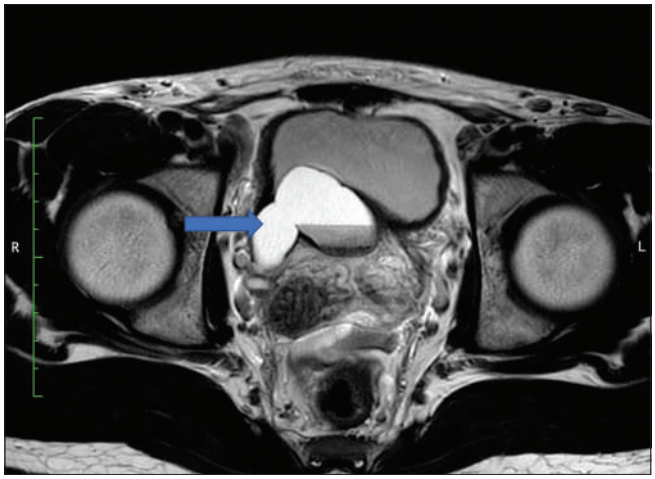

Figure 2: T2-weighted axial section image showing a lobulated cystic lesion at a right posterolateral aspect of the urinary bladder. The cystic lesion shows a fluid debris level, suggesting a seminal vesicle cyst. The cyst is causing compression on the adjacent urinary bladder

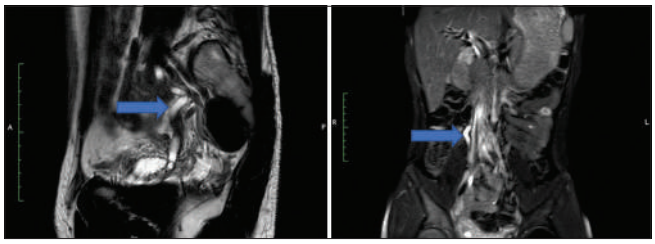

Figure 3: T2-weighted sagittal and a coronal image showing a moderately dilated right ureter with the lumen's upper blind-ending and hyperintense signals

a triad of seminal vesicle cyst, ipsilateral renal agenesis, and ejaculatory duct obstruction, which was first discovered in 1914.[4] Patients present with painful urination, increase urge and frequency to urinate, inflammation of the prostate gland, perineal or scrotal pain, epididymitis, and painful ejaculation. The diagnosis of this syndrome is delayed or missed, because symptoms appear with the beginning of a sexual activity.

Imaging plays an important role in the diagnosis of Zinner syndrome. Different imaging modalities include abdominal ultrasonography, abdominal CT scan, and MRI scan. Cystic

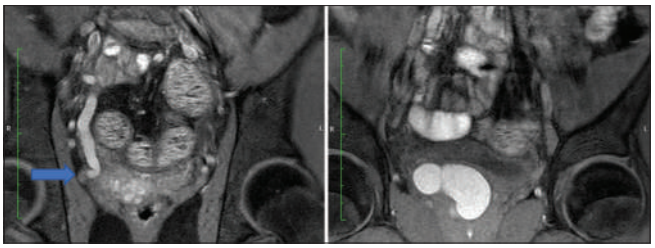

Figure 4: T1-weighted coronal image showing dilated right ureter with ectopic insertion into the right seminal vesicle duct/ ejaculatory duct

lesions are seen on the seminal vesicles. The size and location of the lesions can be estimated with the help of abdominal ultrasonography. The ultrasound also reveals the integrity of the bladder and the lack of the ipsilateral kidney.[5]

Analyses of the cyst contents and authentication of the diagnosis are done with the help of MRI. MRI is considered to be the gold standard in confirming the diagnosis. Cystic lesions are normally hypointense on T1 and hyperintense on T2. Blockage of the ejaculatory ducts can be authenticated, and a complete analysis of the glands can be carried out.[5]

Our case was of a 14-year-old male patient who complained of vague lower abdominal pain and dysuria. Blood and urine examinations were within normal limits. However, the abdominal ultrasound revealed an absent right kidney and an ipsilateral seminal cyst. MRI revealed an absent right kidney, seminal vesicle cyst, and right ejaculatory duct obstruction, confirming the Zinner syndrome diagnosis.

Almofareh *et al.*,[6] in their study, reported Zinner syndrome in a 35-year-old male patient who presented with primary infertility for 10 years, in whom ultrasound revealed an absent right kidney, CT confirmed right renal agenesis and right seminal vesicle cyst. Ibrahimi *et al.*[7] reported the case of a 33-year-old patient who presented with complaints of recurrent dysuria and ejaculatory disorders for the past 5 years in whom imaging studies revealed an empty left renal fossa and a left seminal vesicle which was compatible with the diagnosis of Zinner syndrome. Similarly, in the studies by Militaru *et al.*,[8] Demaeyer *et al.*,[9] Almuhanna *et al.*,[10] Gurung *et al.*,[11] Gorantla *et al.*,[12] Jaganathan *et al.*,[13] and Djidda *et al.*,[5] MRI confirmed Zinner syndrome.

CONCLUSION

With advances in radiology, the diagnosis of Zinner syndrome can be made before the 2nd and 3rd decades. Although uncommon, any doubt should be thoroughly investigated with initial screening by ultrasonography and

confirmation with MRI. The early detection would help the patient relieve the symptoms and prevent complications that may arise due to the same. Disease progression may be arrested and may also improve quality of life. Male patients presenting with uncommon symptoms such as dysuria and infertility without any identifiable cause may be a ground to investigate Zinner syndrome.

REFERENCES

1. Florim S, Oliveira V, Rocha D. Zinner syndrome presenting with intermittent scrotal pain in a young man. Radiol Case Rep 2018;13:1224-7.
2. AlArifi M, Al-Gahwary M, Gomha M. The association of renal agenesis and ipsilateral seminal vesicle cyst: Zinner syndrome case report. Case Rep Urol 2019;2019:1242149.
3. Pereira BJ, Sousa L, Azinhais P, Conceição P, Borges R, Leão R, *et al.* Zinner's syndrome: An up-to-date review of the literature based on a clinical case. Andrologia 2009;41:322-30.
4. Zinner A. A Confusing Diagnosis in the Face of Chronic Disabling Perineoscrotal Pain in the Young Subject, about a Case. Wien Med Wochenschr 1914;64:605-9.
5. Abakar D, Badi FE, Sabiri M, El Manjra S, Lezar S, Essodegui F. Zinner syndrome. Eur J Case Rep Intern Med 2021;8:002628.
6. Almofareh AM, Aljuaid KM, Almirabi SA, Hakami YM, Alwan AM. Zinner syndrome: A case report of a rare etiology of infertility. Cureus 2021;13:e17386.
7. Ibrahimi A, Hosni A, Ziani I, Laamrani FZ, Sayegh HE, Jroundi L, *et al.* Zinner's Syndrome: A rare diagnosis of dysuria based on imaging. Case Rep Urol 2020;2020:8826664.
8. Militaru V, Mihaly ZA, Ilea C, Coman M, Stanciu M, Crisan, N, *et al.* Zinner syndrome-A case report. Med Pharm Rep 2021;94 Suppl No 1:S47-50.
9. Demaeyer L, Holz S, Pamart D, Taylor S, Naudin M. Robotic management of painful Zinner syndrome, case report and review of the literature. Int J Surg Case Rep 2020;73:61-4.
10. Almuhanna AM, Alsuhaibani S, Almesned R, Almatar A, Alali H. Zinner's syndrome: A case report of a rare maldevelopment in the male genitourinary tract. Urol Case Rep 2021;39:101839.
11. Gurung B, Panta OB, Dhakal V, Ghimire RK. Zinner syndrome: A case report of rare urogenital anomaly. J Med Ultrasound 2021;30:59-61.
12. Gorantla R, Allu S, Rao A. Triad of unilateral renal dysgenesis with ipsilateral seminal vesical and ejaculatory duct obstruction: An uncommon urogenital congenital anomaly, Zinner syndrome-a case report. Indian J Radiol Imaging 2021;31:707-9.
13. Jaganathan D, Kathirvelu G, Nagarajan S, Ganesan UN. Rare cause of painful ejaculation-Zinner's syndrome: A case report. Am J Sonogr 2020;3:1.

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Review Article

Role of Nasal Corticosteroids in Allergic Rhinitis

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Abstract

Intranasal corticosteroids are acknowledged as a reliable first-line treatment for allergic rhinitis (AR). There are several intranasal corticosteroids in the market, namely, budesonide, flunisolide, fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide, and mometasone furoate. Each one is effective in preventing persistent AR and treating seasonal AR. In general, they provide relief from rhinorrhea, itching and the early and late stages of an allergic reaction which is marked by sneezing, with studies demonstrating practically total symptom avoidance in the late period. The justification for using topical intranasal corticosteroids to treat allergies is that it is possible to reach sufficient medication concentrations at receptor sites in cases of rhinitis within the nasal mucosa. This results in symptom management and lowers the danger of harmful systemic consequences. The negative effects are typically around the nasal area mucosa, including sneezing, burning, and stinging. Regardless of the formulation, 5–10% of people get headaches and epistaxis. The only differences between treatment agents are potency, patient preference, dosage plans, and the method and mode of distribution.

Key words: Allergic rhinitis, Corticosteroids, Nasal mucosa, Rhinorrhea

INTRODUCTION

Allergic rhinitis (AR) is a persistent inflammatory condition affecting 10–30% of Americans and more than 1 billion individuals globally, with a rising frequency. AR can significantly affect the standard of care for patients due to expensive healthcare. AR can also lead to significant problems and poses a threat to the emergence of asthma. AR is mediated by an antibody condition, where the nasal mucosa is inflamed due to the interplay between allergens and antibodies to immunoglobulin E. This complex attaches to the surface of mast cells, that when activated, produce a variety of inflammatory mediators, causing instantaneous allergy symptoms and an allergic reaction.[1] A common classification for AR is based on the frequency and duration of symptoms. It can be divided into intermittent AR (4 days/month) and persistent AR (PAR) (4 days per week and lasting 4 weeks). It can alter academic performance and may impact a child's ability to focus, in addition to generating stress, a lack of social integration, and a degree of familial dysfunction. Therefore, clinical investigations are crucial to discover a therapy that works well and is safe for use with young patients who have AR.[2]

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Intranasal corticosteroid spray (INCS) is one of the first-line therapies for treating AR since it is the most effective anti-inflammatory medication. Figure 1[3] systematically explains the sensitization process. INCS is beneficial for AR patients, particularly for those with nasal obstruction or moderate-to-severe AR. Proinflammatory gene transcription is inhibited and anti-inflammatory gene transcription is activated by INCS. It, then, prevents the release of cytokines and the invasion of inflammatory cells. According to a study that examined medication-taking behavior in a real-world scenario, although INCS has medical advantages, only 11.3% of patients reporting data from 7–100 days, strictly adhered to the medicine. Use of inhaled corticosteroids on an as-needed basis, in combination with long-acting β-agonists is recommended for treatment of step-two asthma.[4]

An INCS is generally advised for everyday use over an extended period of time, because its accumulating effects peak after at least 2 weeks of use. Clinical symptoms can lessen on the 1st day, and the initial application takes effect 6–24 h thereafter. As a result, even when the symptoms are under control, patients often do not adhere to the prescribed course of action or quit taking the prescription.[4]

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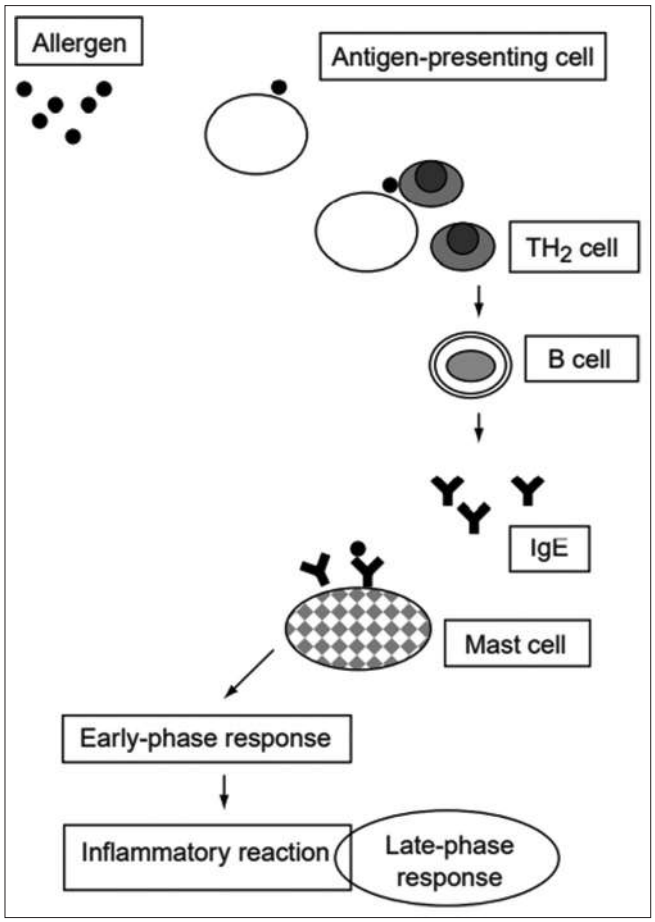

Figure 1: Schematic representation of the sensitization process adapted from Trangsrud *et al.*, the Journal of Human Pharmacology and Drug Therapy. 2002;22(11):1458-67.

The Chinese official followed AR and its Impact on Asthma, 2008, guidelines to advise a first dose of fluticasone furoate nasal spray (FFNS) for adults and adolescents of 110 μg once a day (≥12 years). However, the use of FFNS in Chinese clinical practice is not widespread due to a paucity of data on safety and effectiveness. The study examined the effectiveness and comparing the safety of FFNS with a placebo in a Chinese pediatric population with an age range of 2–12 years. The study reported that FFNS 55 μg or 110 μg has favorable efficacy and safety profiles in Chinese pediatric populations, supporting its usage in clinical treatment for AR children, particularly younger children aged 2–6 years.[2]

A by Hoang *et al.* reported that participants in the low-adherence group (28%) nonetheless experienced a considerable improvement in their overall nasal health when compared to the baseline symptoms. The effectiveness of as-needed INCS in comparison to routine INCS is still up for debate.[4] The current review focuses on the use of corticosteroids in treatment of AR.

OVERVIEW OF TREATMENT OF AR

Better health and the best results depend on individuals taking their medication as prescribed and patient adherence is crucial to the treatment of any disease. Adherence with INCS is essential to effectively control AR over the long term, and non-adherence can get in the way of treatment. Most AR patients should receive treatment before exposure to allergens to manage allergy symptoms. The patient education is necessary to boost compliance with INC therapy, because patients would not be aware of the necessity to take their medication frequently for maintenance rather than only when necessary to try to cure acute symptoms. As previously indicated, avoiding the trigger is the main non-pharmacologic treatment for AR.[1]

TREATMENT DIFFERENT FROM CORTICOSTEROIDS

Second-generation antihistamines are preferable since earlier first-generation antihistamines tend to cause drowsiness, thus restricting their use. Psychomotor-cognitive impairment, confusion, agitation, and anticholinergic symptoms are a few other side effects related to first-generation antihistamines. Clinical research indicates that co-administration of corticosteroids and antihistamines does not appear to confer any long-term advantages over corticosteroids alone, despite the apparent complementary mechanisms of action between the two drugs.[3]

Topical and oral decongestants are α-receptor agonists that cause vasoconstriction of vessels in the nasal mucosa, and thus provide relief of nasal congestion. However, they have no effect on other symptoms such as rhinorrhea, sneezing, or itching. Due to the potential for rebound congestion, or rhinitis medicamentosa, the use of topical decongestants should be restricted to no more than 5 days at a time. If a patient needs treatment over 5 days, oral decongestants should be taken. A benefit of decongestants over antihistamines is that they are effective when taken as needed and do not need to be administered before antigen exposure.[3]

Oral decongestants have several side effects that should be avoided in certain medical conditions, including uncontrolled hypertension, hyperthyroidism, diabetes mellitus, and benign prostatic hyperplasia. The side effects include central nervous system stimulation, cardiovascular stimulation, and urinary retention. The mast cell stabilizer, cromolyn sodium, prevents and treats all nasal symptoms of early-and late-phase responses. The best results come from using it as a preventive measure. It should

be administered daily for several weeks before allergen exposure for the best relief. The majority of people find it relatively safe, with the most common side effect of localized nasal mucosal irritation.[3]

Immunotherapy is a progressive, methodical method of injecting the problematic antigen subcutaneously in increasing doses in an effort to increase immunity toward the antigen. Typically, it is saved for patients with significant symptoms that interfere with daily living activities, whose effects are caused by a small number of recognizable allergens, and who do not benefit from conventional treatments.[3]

Immunotherapy is expensive and could be fatal if an anaphylactic reaction develops. The anti-IgE monoclonal antibody olizumab, indicated for subcutaneous therapy of seasonal AR (SAR) in adults and children, is awaiting approval from the Food and Drug Administration. Olizumab is a monoclonal antibody that is humanized and recombinant that targets circulating IgE. Clinical research suggests that it might help patients who do not respond to corticosteroids or antihistamines, or as an additional therapy.[3]

INCS

Nasal symptoms connected to both early-and late-phase allergic reactions can be efficiently prevented and treated with intranasal corticosteroids. They generally reduce rhinorrhea, sneezing, nasal congestion, and itching. In certain studies, they have been demonstrated to almost entirely eliminate late-phase symptoms. A complete response to the medications could take up to several weeks, even though some relief might start to show in a few days.[3]

Intranasal corticosteroids have a complicated and unclear mechanism of action. Whether the chemicals enter the nasal mucosa or affect the target cells is unknown. Corticosteroids have distinct effects on mediators and inflammatory cells involved in allergic reactions. Leukotrienes, mast cells, and prostaglandins seem to be involved as mediators. The medications also work by preventing the generation of cytokines, activation of eosinophils, and T lymphocytes, particularly TH2 cells. Topical corticosteroids allow sufficient medication concentrations at receptor sites in the nasal mucosa. This helps to regulate symptoms and lowers the possibility of systemic adverse events (AEs). Even though all intranasal corticosteroids currently available are safe and effective for managing AR, it is essential to consider variations in efficacy, side effects, and clinical characteristics. In most cases, the degree of cutaneous vasoconstrictive action from a skin model determines the topical potency of corticosteroids. According to this model, mometasone furoate and fluticasone propionate are two medications that are more effective than other intranasal corticosteroids. Although there is no direct relationship between the degree of vasoconstriction and anti-inflammatory potency, it does describe some of the clinical effectiveness of the medications in AR.[3]

The ability to bind to glucocorticoid receptors is another indicator of potency. According to one study, the order of lowest to highest receptor-binding affinities includes dexamethasone, triamcinolone acetonide, budesonide, fluticasone propionate, and mometasone furoate. In a related investigation, fluticasone's affinity was greater than that of the beclomethasone, dexamethasone, and budesonide active metabolites.[3]

INCs have limited systemic bioavailability and very low rates of systemic AEs, such as growth suppression or the suppression of the hypothalamic-pituitary-adrenal axis, which are occasionally reported with oral steroids.[1]

The most recent practice parameter was created by the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma, and Immunology, with suggestions for clinicians, depending on the quality of the evidence on making treatment decisions for their patients with AR. These guidelines state that INCs are the most efficient single therapy for easing and reducing the symptoms of SAR and persistent AR (PAR) symptoms, including nasal congestion.[1]

Recently, the efficacy of INCS has been evaluated in the treatment of AR. Pediatric AR patients between the ages of 2 and 12 were randomly assigned to receive either FFNS 55 or 110 mg or a placebo in a phase 4, randomized, double-blind, and placebo-controlled trial. Electronic diary cards were filled out to document the symptoms, usage of rescue medications, and treatment compliance. Anterior rhinoscopy and total therapeutic response were assessed and documented.[2]

In this trial, once daily FFNS 55 μg and 110 μg were compared to a vehicle placebo nasal spray to determine their effectiveness and safety in treating juvenile AR patients. Before randomization, there was a treatment-free run-in period (4–14 days), followed by 4 weeks of double-blind therapy and then a 3-7-day treatment-free follow-up period. Figure 2 displays the fluticasone furoate nasal spray FFNS randomization.[2]

In total, 92% of patients finished the study, and 12% of patients in the placebo group discontinued treatment early, compared to 7% in the once daily FFNS 55 μg and once

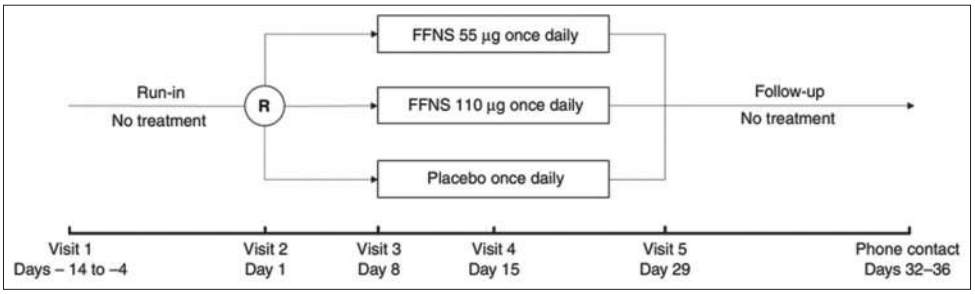

Figure 2: Fluticasone furoate nasal spray randomization

daily FFNS 110 µg groups. Reaching the stopping criterion specified in the protocol was the main cause of the early withdrawal. Overall, data from the intent-to-treat (ITT) sample showed that FFNS 55, 110, and pooled FFNS 55/110 µg had numerically greater LS mean changes from baseline in reflective total nasal symptom score (rTNSS) than placebo. Over the first 2 and 4 weeks, the LS mean difference was statistically significant ($P < 0.001$). There was no statistically significant difference between therapy with FFNS 55 µg and FFNS 110 µg in any age group, according to *post hoc* analyses. The ITT group versus placebo demonstrated the same statistically significant LS mean changes as from baseline in rTNSS in children with moderate and severe baseline nose symptoms ($P < 0.001$). In patients with substantial baseline ocular symptoms, *post hoc* analyses showed that the LS mean changes from baseline in rTOSS were statistically significant between the FFNS 55 µg group and the FFNS 110 µg group throughout the first 4 weeks (−0.06 versus −0.58, $P = 0.046$). A total of 33% of patients treated with FFNS 55 µg and 43% treated with FFNS 110 µg regarded their overall response to therapy as "significantly improved" after the first 2 weeks of treatment.[2]

As opposed to the placebo group, in the subgroup of patients aged 2–6 years, a similar pattern was seen. Substantially, more patients treated with FFNS 55 µg ($P = 0.005$) and FFNS 110 µg ($P < 0.001$) had their overall response to treatment judged by their caregivers as "significantly better" compared to those treated with placebo. After receiving treatment for 4 weeks, this pattern was still present.[2]

Four placebo-controlled studies found that FFNS significantly reduced AR symptoms and had an acceptable safety profile.[1] Fluticasone propionate nasal spray (FPNS) and FFNS were compared, and it was discovered that FFNS was favored over FPNS in terms of aroma, aftertaste and leakage down the throat/nose. According to the findings of two trials, FFNS was generally preferred over mometasone furoate nasal spray.[1]

Since INCs are so effective at preventing and treating the symptoms of both early-and late-phase reactions, they are preferred for PAR, which is defined as occurring more than 4 days per week or 4 weeks per year. The effectiveness of FFNS 110 µg once daily for 2 weeks in adult and adolescent patients with SAR was assessed by a combined analysis of 5 randomized placebo-controlled trials. Compared to the placebo group, there were notable improvements in each patient's specific nasal and ocular symptoms in the FFNS group. These improvements were consistent irrespective of the patient's ethnicity, pollen allergy season or location.[1]

Unpleasant side effects are another major cause for not taking nasal allergy medicine as prescribed. These INC negative effects are primarily sensory in nature and are highly dependent on the characteristics of the device and spray. INCs have a number of sensory qualities that help patients accept the drug and be inclined to adhere to their treatment. These qualities are traits of the drug, including the device and spray itself (such as flavor, aroma, irritability, or leaking).[1]

To compare the effects of as-needed INCS against regular INCS, as-needed antihistamine, or placebo, systematic searches for randomized controlled trials were conducted. TNSS and disease-specific quality of life were the primary objectives (DSQoL). Analysis of subgroups by AR subtype (perennial vs. seasonal), age (adults vs. children), dosage (high vs. low), and INCS systemic bioavailability (old- vs. new-generation formulation) was primary outcomes. INCS with <1% systemic bioavailability was considered new-generation INCS, which included mometasone furoate, fluticasone furoate, fluticasone propionate, and ciclesonide.[4]

In general, the risk of bias in missing outcome data was modest across all eight RCTs. In 75%, 50% and 63% of the included RCTs, respectively, some issues with the randomization process, deviation from intended interventions, and selection of the reported results were discovered. A substantial risk of measurement bias was present in 63% of the evaluated studies.[4]

This comprehensive review and meta-analysis showed that regular INCS use was superior to INCS used only, when necessary, in terms of enhancing TNSS, DSQoL, and nasal patency. These results support the conventional wisdom that the maximum benefits of INCS for clinical improvement can be realized after up to 2 weeks of continuous use. The study showed that the daily reflective TNSS of the subjects who got 110 μg of FFNS considerably increased.[4]

The goal of consistent INCS use is to reduce ongoing inflammation and maintain a long-term control of clinical symptoms. Both patients with SAR and those with persistent AR have been found to have minimal chronic inflammation.[1]

New-generation INCS used on an as-needed basis may benefit from decreased corticosteroid exposure and fewer side effects, especially in the case of pediatric and adolescent populations. The as-needed INCS revealed some advantages that outweighed the disadvantages. Since INCS shows an effect between 6 and 24 h after being administered, the majority of nasal symptoms can be resolved in a single day. A 15-min quick onset was observed when INCS and an intranasal antihistamine were combined, pointing to an alternate on-demand application. These results may help to explain why the majority of patients preferred the as-needed INCS, which is consistent with the low adherence to INCS in real-world settings.[4]

CONCLUSION

When comparing INCs for prevention and treatment of AR symptoms, sensory properties have been demonstrated to affect patient preference. Health-care professionals can help patients understand the value of sensory qualities by giving them advice. In addition, proper use of these medications depends on the patient understanding of how they operate, which should result in more effective pharmacotherapy.

REFERENCES

1. May JR, Dolen WK. Evaluation of intranasal corticosteroid sensory attributes and patient preference for fluticasone furoate for the treatment of allergic rhinitis. Clin Ther 2019;41:1589-96.
2. Zhang Y, Wei P, Chen B, Li X, Luo X, Chen X, *et al*. Intranasal fluticasone furoate in pediatric allergic rhinitis: Randomized controlled study. Pediatr Res 2021;89:1832-9.
3. Trangsrud AJ, Whitaker AL, Small RE. Intranasal corticosteroids for allergic rhinitis. Pharmacotherapy 2002;22:1458-67.
4. Hoang MP, Chitsuthipakorn W, Seresirikachorn K, Snidvongs K. As-needed intranasal corticosteroid spray for allergic rhinitis: A systematic review and meta-analysis. Rhinology 2022;60:242-51.

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Review Article

Levocetirizine in Treatment of Urticaria and Allergic Rhinitis

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Abstract

Allergic rhinitis (AR) and urticaria are the two most common allergic disorders that affect people globally. Nearly 400 million people worldwide have been affected by AR. Increased urbanization and environmental pollutants are some of the causes that lead to an increased prevalence of AR. Second-generation antihistamines like levocetirizine are approved for the treatment of seasonal AR, perennial AR, and chronic idiopathic urticaria in patients aged ≥2 years as oral drop formulations and ≥6 years as tablet formulations. The current work discusses an overview of levocetirizine, its efficacy, and its safety in the treatment of allergic disorders like AR and urticaria.

Keywords: Allergic rhinitis, Efficacy, Levocetirizine, Safety, Urticaria.

INTRODUCTION

Allergy diseases are frequently underestimated in terms of their prevalence and their negative effects on quality of life (QoL). Immunoglobulin E (IgE), which is found on the surface of mast cells and basophils, plays a crucial role in the allergic reaction. These cells become activated when an allergen interacts with IgE and its receptor complex, causing the production of chemicals like histamine that induce allergic symptoms. Allergic rhinitis (AR) and urticaria are one of the most common allergic conditions.[1]

Globally, AR is reported to impact approximately 25% children and 40% of adult. Approximately 80% of AR symptoms develop before the age of 20 years and increases during the age 20–40 years before gradually declining. The occurrence rate of AR in children over the first 5 years of life was reported to be 17.2%, with a peak age at diagnosis between 24 and 29 months (2.5%). Sex-specific differences in the prevalence of AR with male predominance in childhood and a female predominance in adolescents are reported.[2] Other symptoms are itching of the palate, postnasal drip and cough. Figure 1 demonstrates the symptoms of AR.

Urticaria is another prevalent illness. Patients with urticaria frequently experience angioedema, wheals (hives), or both. Typically, angioedema is present in around half of all urticaria cases. Acute conditions are those that have a duration of <6 weeks. It is considered chronic if it lasts >6 weeks or recurs. The symptoms of the disorder could last for months or even years. Up to 15–25% of people may experience acute urticaria at some point in their lives, and the most common causes are virus infections (particularly those that impact the upper respiratory tract), food allergies, and pharmacological side effects.[1]

Antihistamines are used to treat a variety of allergic disorders, such as AR and urticaria, due to the crucial role of histamine in allergic reactions.[1] Levocetirizine is an effective second-generation histamine receptor antagonist. It is reported to function efficiently against AR in children to improve the QoL.[3]

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MECHANISM OF ACTION OF LEVOCETIRIZINE

Non-sedating (second-generation) histamine H1 receptor antagonists are considered to be a principal therapy for allergic disorders. Levocetirizine is the active R-enantiomer of cetirizine, a second-generation, long-acting, selective peripheral histamine H1 receptor antagonist. The antihistaminic properties of racemic cetirizine reside with the R-enantiomer rather than the S-enantiomer. Figure 2 demonstrates the advantages of Levocetirizine.

Levocetirizine showed a longer duration of action after discontinuation of treatment than other antihistamines. Levocetirizine may be more effective than desloratadine, fexofenadine or loratadine in allergy challenge chamber tests. Levocetirizine is an excellent addition to the class of oral H1 receptor antagonists that are used to treat AR and as first-line therapy in urticaria sufferers.[4]

EFFICACY AND SAFETY ASSESSMENT

Desloratadine, levocetirizine, and placebo were assessed in the Yonekura *et al.*[5] three-arm, randomized, double-blind, and crossover design, which compared the effectiveness of various antihistamines in groups of the same participants. 50 individuals with moderate to severe AR caused by Japanese cedar pollen were randomized to receive placebo,

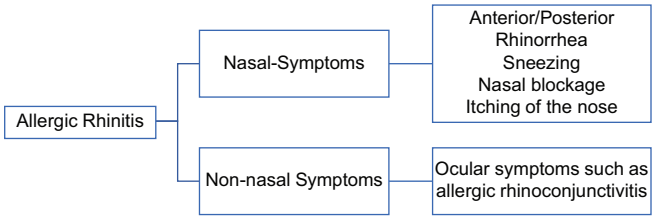

Figure 1: Allergic rhinitis classification

Figure 2: Advantages of levocetirizine

desloratadine (5 mg), or levocetirizine (5 mg). Levocetirizine and desloratadine both significantly outperformed the placebo in terms of controlling symptoms, with a difference in total nasal symptom score (TNSS) from placebo of −2.42 ($P < 0.0001$) for levocetirizine and −1.66 ($P < 0.01$) for desloratadine [Figure 3]. However, there was no statistically significant difference between the two medications. No serious adverse events were reported in the patients.

TNSS: Total nasal symptom score, TOSS: Total ocular symptom score; TNOSS: Total nasal-ocular symptom score, LS mean: Least square mean.

Desloratadine and levocetirizine considerably reduced nasal symptoms in the current randomized, crossover, comparative study in an environmental challenge chamber as compared to placebo, and their safety was also established. Levocetirizine has a tendency to control nasal symptoms more effectively than desloratadine.

Staevska *et al.*[6] evaluated the effectiveness and safety of using levocetirizine and desloratadine, two second-generation antihistamines, up to four times the doses typically indicated for individuals with difficult-to-treat chronic urticaria. The success rate of treatment more than doubled when the medicine dose was increased above the standard 5 mg. Increasing the drug dose above the conventionally prescribed 5 mg for either drug more than doubled the success rate of treatment.

According to this study, at the end of week 3, the overall success rate for the 22 patients taking levocetirizine was significantly ($P < 0.04$) greater than the rate for the 12 patients taking desloratadine. Analysis of the visual analog scores (VAS) for urticaria-related discomfort showed that levocetirizine considerably ($P < 0.003$) outperformed desloratadine in terms of overall improvement. Increasing doses of levocetirizine and desloratadine both improved QoL; however, levocetirizine proved to be superior. With either medicine, there were no severe or serious side effects that resulted in stopping the course of treatment.

In young atopic children, Simons[7] evaluated the possibility that the piperazine H1-antihistamine levocetirizine would have a similar safety profile to a placebo. For 18 months, 510 atopic children between the ages of 12 and 24 months were given levocetirizine 0.125 mg/kg twice a day or a placebo. The treatment groups were similar demographically, and with regard to number of children with: One or more adverse events (levocetirizine, 96.9%; placebo, 95.7%). This study confirmed the safety of levocetirizine in young atopic children. Levocetirizine's therapeutic effectiveness

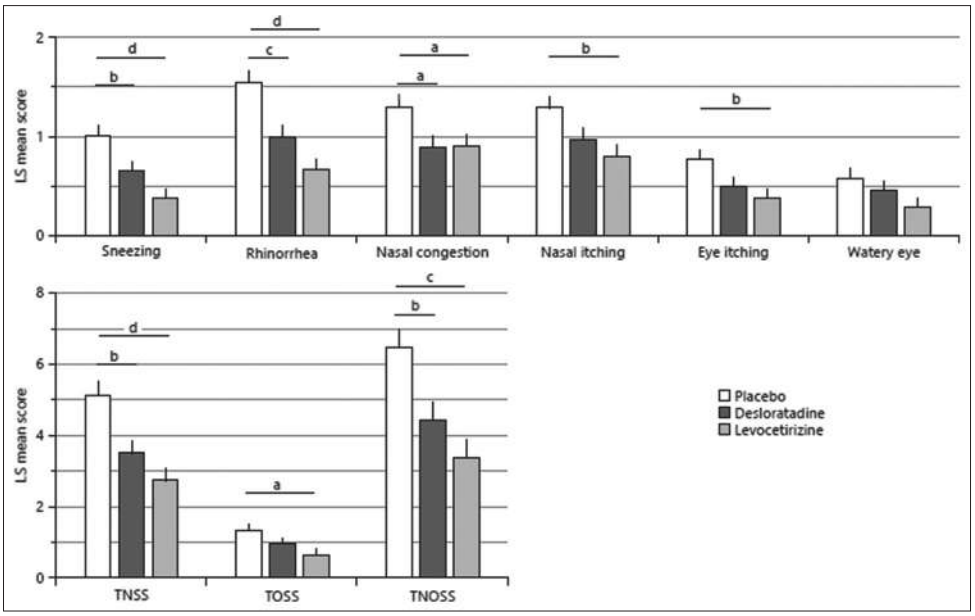

Figure 3: Comparison of mean symptom scores from 120 to 180 min in environmental challenge chamber. Values represent means ± SE. [a]*P* < 0.05, [b]*P* < 0.01, [c]*P* < 0.001, [d]*P* < 0.0001 versus placebo group

and safety in AR and skin allergies were reported by Hair *et al.*[4] This indicates that levocetirizine's therapeutic effectiveness in the treatment of seasonal AR, perennial AR, persistent AR (PER), and chronic idiopathic urticaria (CIU) has been established.

Allergen challenge chamber studies revealed that patients who received levocetirizine had a significantly greater reduction in major symptom complex (MSC) scores from baseline in comparison to fexofenadine, desloratadine, and loratadine. Primary end points showed a significantly greater reduction in MSC scores in the levocetirizine group than in the fexofenadine group at 22–24 h post-dose. At 24–26, and 28 h post dose, the minimization in MSC scores from baseline compared to placebo was significantly ($P < 0.001$) higher in patients who received levocetirizine (2.26 and 2.33) than fexofenadine (0.98 and 1.00).

In comparison to other antihistamines, levocetirizine has a longer duration of antihistaminic effect. In addition, it also resulted in a greater reduction in histamine-induced nasal temperature rise than fexofenadine. Levocetirizine 5 mg reduced the histamine-induced nasal temperature in healthy people more effectively than fexofenadine 120 mg, 24 h after the treatment (0.32 vs. 0.44°C increase; $P = 0.024$).[4]

CONCLUSION

The treatment of allergic disorders such AR and CIU with levocetirizine is successful and generally well tolerated. According to allergen challenge chamber studies, levocetirizine has better efficacy than desloratadine, or fexofenadine. Overall, levocetirizine is a beneficial addition to the oral H1 receptor antagonists currently used to treat AR and as first-line therapy in patients with CIU.

Dr. S K Srivastav
Skin and VD (Ex HOD, DMCH, Laheriasarai), Darbhanga, Bihar

Levocetirizine controls urticaria and is also effective in controlling allergies and other dermatological conditions. I have observed that it has better efficacy than other antihistamines. According to me, Levocetirizine and Fexofenadine provide an equal level of 24-h-long-lasting relief; however, Bilastine is less effective than the former drugs. As per the latest guidelines, 2nd generation H1-antihistamines are strongly recommended for all patients with urticaria, regular use of these is suggested for chronic urticaria. Before considering any other treatment, a 4-fold up dosing of 2nd generation H1-antihistamines is recommended. Current guidelines oppose the simultaneous use of multiple antihistamines. Due to good safety, tolerability and efficacy, Levocetirizine is preferred over other antihistamines.

Dr. Rajeev Setia
M.S. (ENT), Hanumangarh, Rajasthan

I found Levocetirizine efficacious in AR and other respiratory allergies. It is more potent and better in terms of efficacy and safety as compared to other antihistamines. Levocetirizine provides long-lasting effects and has lesser

side effects and quick onset of action. Levocetirizine, in my opinion, offers the finest 24-h-long-lasting relief. It is safe to use for long-term treatments. I believe low-dose levocetirizine provides better safety and tolerability in different types of respiratory allergies. Levocetirizine improves the QoL by providing better relief from symptoms of respiratory allergies with fewer side effects. I have found better results with Levocetirizine as compared to other antihistamines.

Dr. Vinayak Revenkar
M.B.B.S., DNB (Pediatrics), Solapur, Maharashtra

AR has the worst impact on the QoL and sleep of children. As per the Early Prevention of Asthma in Atopic Children (EPAAC) study, Levocetirizine can safely be used for 18-month therapy in children who were in the age group of 12–24 months. Levocetirizine did not have any side effects on developmental milestones and other clinical parameters. In my opinion, Levocetirizine is a better choice for symptom control as compared to Fexofenadine over 24 h among children. As per my knowledge, a good pharmacological treatment option must have a coating of unionized Montelukast to prevent any interaction of stomach acids with Levocetirizine. There should not be any cross-reaction between Levocetirizine and the coating of Montelukast. The coating must not precipitate in the acidic environment of the stomach as it will affect the bioavailability of the drug. Overall, Levocetirizine provides promising results in the management of acute and perennial AR in children.

Dr. Jyoti Dhawan
M.B.B.S., M.D. (Dermatology), Delhi

As per my experience, Levocetirizine provides excellent efficacy in urticaria and other dermatological allergic conditions with superiority over other antihistamines. Levocetirizine is far more efficient in providing 24-h-long-lasting relief when compared to Bilastine and Fexofenadine. The use of 2nd generation H1-antihistamines is strongly advised for all patients with urticaria, and frequent usage is advised for those with chronic urticaria, according to the most recent guidelines. Second-line treatment is advised to start with a 4-fold up-dosing of second-generation H1-antihistamines before considering any other options. Multiple antihistamines taken at once are discouraged by current guideline recommendations. Although it causes sedation in a few patients, due to its safety and tolerability, Levocetirizine is my first choice in patients with urticaria.

Dr. Tushar Anand Shinde
M.B.B.S., DDV, Pune, Maharashtra

Levocetirizine is an efficacious and safe option for treating allergies and dermatological disorders as well as urticaria. I found that it worked more effectively than other antihistamines as it causes less sedation. Levocetirizine, in my opinion, offers the finest 24-h-long-lasting relief; whereas, Fexofenadine and Bilastine are less efficient. The use of 2nd generation H1-antihistamines is strongly recommended for all patients with urticaria, and frequent usage is advised for those with chronic urticaria, according to the most recent guidelines. Second-line treatment is advised to start with a 4-fold up-dosing of second-generation H1-antihistamines before considering any other options. Multiple antihistamines taken at once are discouraged by current recommendations. Levocetirizine is safe, efficacious, and useful in day-to-day dermatological practice.

Dr. Deepak Kumar Gupta
M.B.B.S., MD (Pediatrics), Delhi

Children with AR experience the worst effects on their sleep and QoL. According to the EPAAC trial, children between the ages of 18 and 24 months can safely receive Levocetirizine treatment for 18 months. The adverse effects of Levocetirizine on developmental milestones and other clinical indicators are not significant. Levocetirizine, in my opinion, is superior to Fexofenadine for symptom management. According to me, a proper pharmaceutical regimen must include unionized Montelukast as a coating to avoid any potential stomach acid–Levocetirizine interactions. It consistently produces great outcomes in the treatment of both acute and perennial AR in children.

Dr. Ojas Deokate
MD, DCH, Solapur, Maharashtra

The worst sleep and QoL consequences are experienced by children with AR. Levocetirizine medication for 18 months is safe for children between the ages of 12 and 24 months, according to the EPAAC trial. Levocetirizine had no negative effects on developmental milestones or other clinical markers. I believe that Levocetirizine is a better alternative for treating symptoms than Fexofenadine. According to me, a proper pharmaceutical regimen must include unionized Montelukast as a coating to avoid any potential stomach acid–Levocetirizine interactions. The coating of Montelukast and Levocetirizine should not interact in any way. The coating must not precipitate in the stomach's acidic environment because this will decrease the drug's bioavailability. As per my experience, Levocetirizine is efficacious and has a high safety profile even in long run.

Dr. Mukesh Ruparelia
MD (Skin), Rajkot, Gujarat

I believe that Levocetirizine provides excellent efficacy in the treatment of urticaria and other dermatological

allergies, unlike other antihistamines. Levocetirizine is more effective in providing 24-h-long-lasting relief when compared to other molecules such as Bilastine and Fexofenadine. Second-line treatment is recommended to start with a 4-fold up-dosing of second-generation H1-antihistamines before considering any other options. Levocetirizine provides excellent safety and tolerability.

Dr. T V Ramanikanth
FRCS (Edin), FRCS (Glasgow), DLO, Coimbatore, Tamil Nadu

Levocetirizine is useful and efficacious for the treatment of AR. It has higher efficacy than other antihistamines. It shows quick action in reducing eye and nose symptoms of seasonal and perennial rhinitis with better efficacy than other 2nd generation antihistamines. Levocetirizine is far more efficient in providing 24-h-long-lasting relief when compared to Fexofenadine. It is relatively safe; however, some patients complain of drowsiness despite the drug being non-sedative. Patients had good compliance except for a few who experienced drowsiness after daytime consumption of Levocetirizine. This drug also improves the QoL in patients with AR. Overall clinical experience with Levocetirizine is excellent.

Dr. J Muni. Sekhar
MD (Pediatrics), Tirupati, Andhra Pradesh

Children with AR experience the worst sleep and QoL effects. The EPAAC trial was conducted involving atopic children in the age group of 12–24 months. Clinical indicators or developmental milestones were not adversely affected by levocetirizine. I think Fexofenadine is not as effective in treating symptoms as Levocetirizine. Montelukast coating must not precipitate in the acidic environment of the stomach, as it will reduce the drug's bioavailability. Overall, patients had a good experience and better relief.

Dr. Rakesh
MD (Pediatrics), Chennai, Tamil Nadu

As per my experience, children with AR have a moderate impact on QoL and quality of sleep. The EPAAC trial is a randomized double-masked trial involving 510 atopic children who were in the age group of 12–24 months. As per my opinion, Levocetirizine provides moderate 24-h-long-lasting relief. According to me, a good pharmacological treatment must offer a coating of unionized Montelukast to prevent any interaction of stomach acids with Levocetirizine. This drug has decreased the recurrence of rhinitis in children.

Dr. V Sivaraman
MD (Skin and STI), Pondicherry

Levocetirizine is a reliable and easy-to-use treatment for urticaria and other dermatological allergies. It works better than other antihistamines. However, I would say that Levocetirizine, Fexofenadine and Bilastine equally provide 24-h-long-lasting relief. The use of 2nd generation H1-antihistamines is strongly advised for all patients with urticaria, and frequent use is advised for those with chronic urticaria, according to the most recent guidelines. Second-line treatment is advised to be initiated with a 4-fold up dosing of second-generation H1-antihistamines before considering any other options. Multiple antihistamines taken at once are discouraged by current guideline recommendations. Levocetirizine has acceptable safety and tolerability with minimal sedation. Overall, it is a useful molecule for the first-line management of chronic and spontaneous urticaria.

Dr. S Satheeshkumar
M.B.B.S., DCH, Tirupur, Tamil Nadu

AR somewhat impacts the QoL and sleep in children. Levocetirizine can be administered in children aged between 12 and 24 months without risk, according to the EPAAC trial. The adverse effects of levocetirizine on developmental milestones and other clinical indicators were non-existent. Levocetirizine, in my opinion, is a better option for managing symptoms than Fexofenadine. According to me, effective pharmaceutical treatment must include unionized Montelukast as a coating to avoid any possible interactions between stomach acids and levocetirizine. The coating of Montelukast and Levocetirizine should not interact in any way. To prevent the drug's bioavailability from getting affected, the coating must not precipitate in the stomach's acidic environment. Overall, the use of Levocetirizine shows excellent clinical outcomes in the management of acute and perennial AR.

Dr. Abdul Vahid Maniyar
M.B.B.S., DCH, Hubli, Karnataka

My experience has shown that AR in children has a moderate effect on their QoL and sleep. Levocetirizine can be given to children between the ages of 12 and 24 months for 18 months without any negative side effects, according to the EPAAC experiment. Levocetirizine had no detrimental effects on clinical signs or developmental milestones. I believe Levocetirizine is more useful in treating symptoms than Fexofenadine. In a pharmacological treatment, I would prefer coated and unionized montelukast to prevent Levocetirizine and stomach acid interaction. There should not be any interaction between Levocetirizine and montelukast. The coating must not precipitate in the stomach's acidic environment as it affects the drug's bioavailability. Levocetirizine is more effective than any other antihistamine.

Dr. J K Shashi Rekha
M.B.B.S., DO, Hyderabad, Telangana

I would grade Levocetirizine as a very effective and safe treatment option for urticaria and other dermatological allergies and conditions. Compared to other antihistamines it causes less drowsiness and adjustments of the dose are also possible. I think Fexofenadine is not as effective in treating symptoms as Levocetirizine and Bilastine. Before pursuing any other options, second-line treatment is advised to begin with a 4-fold up dosing of second-generation H1-antihistamines. Levocetirizine is a well-tolerated and safe treatment option. The overall clinical experience has been good with Levocetirizine.

Dr. Chowda Reddy
M.B.B.S., MD (Pediatrics), Bengaluru, Karnataka

AR has a noticeable impact on the QoL and sleep of children. According to the EPAAC trial, children between the age of 12 and 24 months can safely receive levocetirizine treatment for 18 months. Levocetirizine, in my opinion, is a superior option to Fexofenadine for symptom management. According to me, a proper pharmaceutical regimen must include unionised Montelukast as a coating to avoid any potential stomach acid–Levocetirizine interactions. The coating of Montelukast and Levocetirizine should not interact in any way. The coating must not precipitate in the stomach's acidic environment as it reduces the drug's bioavailability. Levocetirizine is a good, safe and cost-effective drug that can be used in long-term treatment.

Dr. Neeraj Tripathi
M.B.B.S., DCH, New Delhi

Children with AR experience the worst sleep and QoL effects. The EPAAC trial found that giving Levocetirizine to children between the age group of 12 and 24 months is safe for 18-month treatment. Clinical indicators or developmental milestones were not adversely affected by Levocetirizine. I think levocetirizine shows better symptom control effectiveness than Fexofenadine. In my opinion, a proper medication regimen must contain unionized Montelukast as a coating to prevent any possible interactions between stomach acid and Levocetirizine. In my clinical practice, levocetirizine has given excellent results in the treatment of acute and perennial AR in children.

Dr. Kailash Chandra Khatri
M.D., Rajasthan

Levocetirizine gives excellent results in urticaria, eczema and other dermatological allergic conditions. It has good efficacy as compared to other antihistamines. All three drugs, i.e. Levocetirizine, Fexofenadine, and Bilastine had similar rates of 24-h long-lasting relief. As per the latest guidelines, 2nd generation H1-antihistamines are strongly recommended for all patients with urticaria, regular use of these is suggested for chronic urticaria. Levocetirizine can be given to children between the ages of 12 and 24 months for 18 months without any negative side effects. Levocetirizine had no detrimental effects on clinical signs or developmental milestones. I have treated many patients with Levocetirizine as it has a good safety profile over other antihistamines.

Dr. Manju Aishwarya
MD, DVL, Salem, Tamil Nadu

As per my experience, levocetirizine is highly efficacious in the treatment of urticaria and other dermatological allergies when compared to other antihistamines. Levocetirizine has the highest rate of 24-h-long-lasting relief, whereas, bilastine has moderate and Fexofenadine shows the worst relief. According to the most recent recommendations, 2nd generation H1-antihistamines are strongly advised for all individuals with urticaria, and frequent use is advised for chronic urticaria. Second-line treatment is advised to start with a 4-fold up-dosing of second-generation H1-antihistamines before considering any other options. Multiple antihistamines taken at once are discouraged by current recommendations. As per my experience, the safety profile of this drug is good as none of the patients reported any side effects apart from mild sedation. Tolerability was also good. Lastly, the overall clinical experience was very good when compared with other antihistamines.

Dr. I Shrikanth Rao
M.B.B.S., DCH, Puttur, Karnataka

Children who suffer from AR experience a moderately high reduction in sleep and QoL. According to the EPAAC research, Levocetirizine can be administered safely for 18 months of therapy in children who were in the age range of 18–24 months. The adverse effects of levocetirizine on developmental milestones and other clinical indicators were not significant. Levocetirizine, in my opinion, is a superior option to Fexofenadine for symptom management. According to me, a proper pharmaceutical regimen must include unionized Montelukast as a coating to avoid any potential stomach acid–Levocetirizine interactions. The coating of Montelukast and Levocetirizine should not interact in any way. Levocetirizine is a well-tolerated and safe drug with superior efficacy to other antihistamines in the management of acute and perennial AR conditions.

Dr. D Yuvaraj Kumar
M.B.B.S., DVD, Tamil Nadu

My overall experience with Levocetirizine has been that this is an effective, sustainable and faster-acting drug for the treatment of urticaria and other dermatological allergic issues. The rate of 24-h-long-lasting relief is the most after

using levocetirizine which declines with fexofenadine and bilastine. According to the most recent recommendations, 2nd generation H1-antihistamines are strongly advised for all patients with urticaria, and consistent use of these is advised for chronic urticaria. Before considering any other options, second-line treatment is advised to begin with a 4-fold up-dosing of second-generation H1-antihistamines. The use of many antihistamines at once is discouraged by current recommendations. In my opinion, it is the safest and most well-tolerated molecule which provides higher convenience over other antihistamines in terms of dosage adjustments.

Dr. K Vishnu Bhat
M.B.B.S., DVD, Kasaragod, Kerala

In patients with urticaria and other dermatological allergic conditions, levocetirizine has good treatment efficacy and is superior to other antihistamines. Fexofenadine, bilastine, and levocetirizine provide equal 24-h-long-lasting relief. As per the latest guidelines, 2nd generation H1-antihistamines are strongly recommended for all patients with urticaria, regular use of these is suggested for chronic urticaria. Overall, it is a safe drug and I have had an excellent clinical experience while treating patients with it.

Dr. T R Dayananda
M.B.B.S., FRUGHS, DHA, Mysore, Karnataka

In my opinion, Levocetirizine has become an over-the-counter medication in patients with urticaria and other dermatological allergic conditions, due to its good efficacy. It has an effective action mechanism and provides relief from itching; it also causes drowsiness. Levocetirizine has the highest for 24-h-long-lasting relief compared to Fexofenadine and Bilastine. As per the latest guidelines, 2nd generation H1-antihistamines as first-line treatment is strongly recommended for all patients with urticaria. Levocetirizine has good safety and tolerability profile, and patient compliance is also fairly good.

Dr. Shivakumar K Patil
M.B.B.S., MD, Belgaum, Karnataka

As per my experience, levocetirizine has excellent efficacy and is more effective than other histamines in the treatment of urticaria and dermatological allergic conditions. I would rank Levocetirizine the highest for providing 24-h-long-lasting relief, whereas fexofenadine and bilastine cannot be rated equally. According to the most recent recommendations, all patients with urticaria should be prescribed 2nd generation H1-antihistamines as the first-line treatment, and those with chronic urticaria should use them frequently. Before pursuing any other options, second-line treatment is advised to begin with a 4-fold up dosing of second-generation H1-antihistamines. Current recommendations discourage taking multiple antihistamines at once. In my opinion, Levocetirizine is a safe drug and I have had a satisfactory clinical experience with this drug.

Dr. Ajay Krishnan
M.B.B.S., M.D., Kottayam, Kerala

Levocetirizine has better efficacy in treating patients with urticaria and other dermatological allergic conditions when compared with other antihistamines. Fexofenadine and Bilastine provide equal 24-h-long-lasting relief but Levocetirizine is superior to both. Second-line treatment is advised to start with a 4-fold up-dosing of second-generation H1-antihistamines before considering any other options. This drug is well tolerated and I have good overall clinical experience with this drug.

Dr. T P Thankappan
M.B.B.S., MD, Thiruvalla, Kerala

Levocetirizine is effective in the treatment of urticaria and other dermatological allergies. It is also superior to other antihistamines. Fexofenadine and Bilastine provided equal 24-h-long-lasting relief but levocetirizine is slightly better than both. The most recent guidelines state that 2nd generation H1-antihistamines should be used by all urticaria patients, especially those with chronic urticaria. Second-line treatment is advised to start with a 4-fold up dosing of second-generation H1-antihistamines before other options are considered. The practice of taking several antihistamines at once is currently discouraged. Levocetirizine is a safe drug with an overall good clinical experience.

Dr. Ananth Reddy
MD, Pediatric, Vemulawada, Telangana

Children with AR experience moderate effects on their sleep and QoL. According to the EPAAC trial, children between the ages of 12 and 24 months can safely receive levocetirizine treatment for 18 months. There were no significant adverse effects of levocetirizine on developmental milestones and other clinical indicators. Levocetirizine, in my opinion, is superior to Fexofenadine in symptom management. According to me, a proper pharmaceutical regimen must include coated and unionized Montelukast to avoid any potential stomach acid–Levocetirizine interactions. The coating of Montelukast and Levocetirizine should not interact in any way. The coating must not precipitate in the acidic environment of the stomach as it will cut down the bioavailability of the drug. Levocetirizine is the best antihistamine for treating AR in patients aged below 12 years. Moreover, it relieves all symptoms such as sneezing, itchy nose, rhinorrhea, and itchy and watery eyes.

Dr. Venkateshwar Gande
MS, ENT, Jagtial, Telangana
Levocetirizine is a better treatment option with superior efficacy at 24 h. It is more efficacious than other antihistamines as it works for 24 h whereas other drugs work such as fexofenadine and Desloratadine work only for 12 and 6 h, respectively. Levocetirizine also provides better relief compared with Fexofenadine. It is a "B" category drug with high tolerability. It is a first-line treatment option for AR and its comorbidities. Levocetirizine starts acting within 1 h and its effects last for 24 h, it provides long-lasting relief and improves the QoL. Importantly, Levocetirizine does not have any drug-to-drug interactions.

Dr. Raghavendra Kumar
M.B.B.S. (Pediatrics), Mahabubnagar, Telangana
My experience has shown that in children, AR has a moderate effect on the QoL and sleep. Levocetirizine for 18 months is safe for children aged 12–24 months, according to the EPAAC trial. Levocetirizine had no negative effects on developmental milestones or other clinical markers. I believe that Levocetirizine is a better alternative for treating symptoms than Fexofenadine. In my opinion, a proper medication regimen must contain unionized montelukast as a coating to prevent any possible interactions between stomach acid and Levocetirizine. Levocetirizine and Montelukast should not interact in any way. To prevent affecting the bioavailability of the drug, Montelukast coating must not precipitate in the acidic environment of the stomach. Levocetirizine has a faster onset of action (1 h) and provides long-lasting relief (24 h).

Dr. Shrikant K Sutar
M.B.B.S., DCH, Kolhapur, Maharashtra
In my practice, I have observed that children with AR suffer greatly in terms of their QoL and sleep. The EPAAC trial found that for children between the age of 12 and 24 months, levocetirizine is safe for 18 months. Clinical indicators or developmental milestones were not adversely affected by levocetirizine. I think Fexofenadine is not as effective as Levocetirizine in treating symptoms. In my opinion, to prevent any potential interactions between stomach acid and levocetirizine, unionized Montelukast should be used as a coating in an appropriate drug regimen. Due to the opposite nature of drugs, levocetirizine, and montelukast should not interact in any way. The coating must not precipitate in the acidic environment of the stomach because it will reduce the drug's bioavailability. Levocetirizine provides good results and improves the QoL in children with acute and perennial AR.

Dr. Sanjay Fernandes
MD, DNB, DPV, Mumbai, Maharashtra
Levocetirizine is effective in the treatment of urticaria and other dermatological allergic conditions. It also has a quicker onset of action compared to other antihistamines. Fexofenadine and Bilastine provide equal 24-h long-lasting relief whereas levocetirizine is slightly better than both. Second-line treatment is advised to start with a 4-fold up-dosing of second-generation H1-antihistamines before considering any other options. Finally, it is a safe and well-tolerated drug and I have good clinical experience with it.

Dr. Karan Shah
MD, DVD, Kalyan, Maharashtra
In my advice, Levocetirizine is a good and effective treatment for urticaria and other dermatological allergic conditions. It is better than Fexofenadine and desloratadine. Levocetirizine performs better than both Fexofenadine and Bilastine in terms of 24-h-long-lasting relief. According to the most recent recommendations, all patients with urticaria should use 2nd generation H1-antihistamines, and those with chronic urticaria should use them routinely. Before weighing any other choices, it is indicated that second-line treatment begins with a 4-fold up-dosing of second-generation H1-antihistamines. Current recommendations discourage taking multiple antihistamines at once. Levocetirizine has a good safety and tolerability profile over other antihistamines. The overall clinical experience was very good with levocetirizine.

Dr. Sandeep U Buddhadeo
M. Derm, DVD, Bhiwandi, Maharashtra
Levocetirizine is a good and effective antihistamine that works well with urticaria and the majority of itchy skin disorders. I believe it has little sedative effects which help in relieving pruritis faster. In terms of 24-h-long-lasting alleviation, Levocetirizine performs marginally better than Fexofenadine and Bilastine. The most recent guidelines state that 2nd generation H1-antihistamines should be used by all urticaria patients, especially those with chronic urticaria. It is advised that second-line treatment starts with a 4-fold up dosing of second-generation H1-antihistamines before assessing any other options. The practice of taking several antihistamines at once is currently prohibited. It is a safe drug with mild sedation for a day or two in some patients. The overall clinical experience has been good.

Dr. Kompal Agarwal
M.B.B.S., MD, Rewa, Madhya Pradesh
As per my experience, Levocetirizine has an average treatment efficacy for treating urticaria and other dermatological allergies. It has better efficacy than Fexofenadine; less efficacy than Bilastine and Hydroxyzine. According to me, levocetirizine is more effective in providing 24-h-long-lasting relief when compared to fexofenadine. According to the most recent recommendations, all urticaria patients, especially those with chronic urticaria, should take 2nd generation H1-antihistamines. Before

considering any other options, it is indicated that second-line treatment begins with a 4-fold up dosing of second-generation H1-antihistamines. The current guidelines strongly suggest against the use of multiple antihistamines at once. Levocetirizine has a safe and tolerable profile and gives good clinical experience.

Dr. Sudhanshu Dixit
M.B.B.S., MS (ENT), Rewa, Madhya Pradesh

In my opinion, Levocetirizine is the most effective and safe option for AR treatment. It is more effective than all other antihistamines. Patients show more compliance with the dosing of Levocetirizine. I think Fexofenadine is less effective in treating symptoms than Levocetirizine. It is also safe to be used in children. It provides 24 h of efficacy with a single dose. It has a good impact on QoL. Levocetirizine is a good and safe molecule for the management of AR.

Dr. Rajeev Kaura
MD, DCH, Durg, Chhattisgarh

I have observed that AR in children has a moderate effect on the QoL and sleep. According to the EPAAC trial, children between the age group of 12 and 24 months can safely receive Levocetirizine treatment for 18 months. The adverse effects of levocetirizine on developmental milestones and other clinical indicators were nonexistent. Levocetirizine is a superior option to Fexofenadine for symptom management. According to me, a proper pharmaceutical regimen must include unionized Montelukast as a coating to prevent any potential stomach acid–Levocetirizine interactions. The coating of Montelukast and Levocetirizine should not interact in any way. The coating must not precipitate in the acidic environment of the stomach as it will downgrade the bioavailability of the drug. It is a drug of choice in the treatment of acute and perennial AR among children.

Dr. Aparna Gaikwad
M.B.B.S., DNB, MNAMS (Dermatology), Nashik, Maharashtra

Levocetirizine has very good efficacy in the management of urticaria and other dermatological allergic conditions. This drug is more efficacious than other antihistamines with very less sedation. Levocetirizine is more effective in providing 24-h-long-lasting relief when compared to other molecules such as Bilastine and Fexofenadine. According to the most recent recommendations, all patients with urticaria should use 2nd generation H1-antihistamines, and those with chronic urticaria should use them frequently. Before weighing any other choices, it is indicated that second-line treatment begins with a 4-fold up dosing of second-generation H1-antihistamines. Current recommendations restrict taking multiple antihistamines at once. Levocetirizine has a good safety profile and is well-tolerable. It provides excellent clinical experience.

Dr. Rasika Shivarkar
M.B.B.S., DDV, Pune, Maharashtra

Levocetirizine has good efficacy in the treatment of urticaria and other dermatological allergies. It is also superior to other antihistamines. I think Bilastine is less effective in providing 24-h long-lasting relief as compared to Fexofenadine and Levocetirizine. As per my understanding, the latest guidelines suggest that 2nd generation H1-antihistamines are strongly recommended for all patients with urticaria. Essentially, Levocetirizine has a good safety and tolerability profile with good overall clinical experience.

Dr. Pradeep Tandon
M.B.B.S., DCH, MRSH, New Delhi

Children with AR experience the worst effects on their sleep and QoL. According to the EPAAC trial, children between the ages of 12 and 24 months can safely receive levocetirizine treatment for 18 months. The adverse effects of levocetirizine on developmental milestones and other clinical indicators were non-significant. Levocetirizine, in my opinion, is a superior option to Fexofenadine for symptom management. According to me, a proper pharmaceutical regimen must include coated and unionized Montelukast to prevent any potential stomach acid–Levocetirizine interactions. The coating of Montelukast and Levocetirizine should not interact in any way. The coating must not precipitate in the stomach's acidic environment because this will decrease the drug's bioavailability. Levocetirizine, in my opinion, shows a good and satisfactory response in the treatment of both acute and perennial AR in children.

Dr. Deepak Gandhi
DNB (pediatrics), Mumbai, Maharashtra

Children with AR experience the worst sleep and QoL effects. The EPAAC trial found that for children aged 12–24 months, levocetirizine is safe for 18 months. Clinical indicators or developmental milestones were not adversely affected by levocetirizine. I think Fexofenadine is inferior in treating symptoms as compared to Levocetirizine. I believe that unionized Montelukast should be used as a coating as part of a proper medication regimen to prevent any possible interactions between stomach acid and levocetirizine. There should not be any interaction between Levocetirizine and Montelukast. Since it will reduce the drug's bioavailability, the coating must not precipitate in the acidic environment of the stomach. Levocetirizine offers faster and more consistent relief from allergic symptoms. It is also safe for long-term treatment.

REFERENCES

1. Wang XY, Lim-Jurado M, Prepageran N, Tantilipikorn P, Wang DY. Treatment of allergic rhinitis and urticaria: A review of the newest

antihistamine drug bilastine. Ther Clin Risk Manag 2016;12:585-97.
2. Husna SM, Tan HT, Shukri NM, Ashari NS, Wong KK. Allergic rhinitis: A clinical and pathophysiological overview. Front Med (Lausanne) 2022;9:874114.
3. Zheng PJ, Wang JS, Liu GF, Zhang SH, Zhang YY. Efficacy of levocetirizine for the treatment of children with allergic rhinitis: A protocol for systematic review and meta-analysis. Medicine (Baltimore) 2020;99:e20557.
4. Hair PI, Scott LJ. Levocetirizine: A review of its use in the management of allergic rhinitis and skin allergies. Drugs 2006;66:973-96.
5. Yonekura S, Okamoto Y, Sakurai D, Iinuma T, Sakurai T, Yoneda R, *et al*. Efficacy of desloratadine and levocetirizine in patients with cedar pollen-induced allergic rhinitis: A randomized, double-blind study. Int Arch Allergy Immunol 2019;180:274-83.
6. Staevska M, Popov TA, Kralimarkova T, Lazarova C, Kraeva S, Popova D, *et al*. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. J Allergy Clin Immunol 2010;125:676-82.
7. Simons FE. Early Prevention of Asthma in Atopic Children (EPAAC) Study Group. Safety of levocetirizine treatment in young atopic children: An 18-month study. Pediatr Allergy Immunol 2007;18:535-42.

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Original Article

A Comparative Study on the Efficacy and Safety Profile of Bupivacaine versus Ropivacaine for Intrathecal Anesthesia in Lower Abdominal and Lower Limb Surgeries – A Prospective Randomized Controlled Study

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Abstract

Background: Ambulatory anesthesia's primary goal is fast healing, leading to the early hospital discharge with minimal post-operative side effects. The present study compared the intrathecal administration of 3 mL of 0.75% isobaric ropivacaine with 3 mL of 0.5% hyperbaric bupivacaine on these parameters on the onset duration, hemodynamic stability, and side effects of anesthesia.

Materials and Methods: This study enrolled 60 patients. They were between 18 and 75 years old and over 160 cm tall. Under spinal anesthesia, they underwent elective lower abdominal and lower limb surgeries. This prospective, randomized, and controlled study compared the onset, duration, hemodynamic stability, and side effects of the subarachnoid block between 0.5% bupivacaine hyperbaric and 0.755% ropivacaine isobaric.

Results: In Group B (2.17 ± 0.26 min), the onset of sensory blockade was rapid, whereas, in Group R (6.76 ± 0.19 min), it was delayed. Regression of sensory blockade lasted significantly longer in Group B (102 ± 10.88 min) than in Group R (58 ± 11.73 min), which was clinically significant ($P < 0.0001$). In Group B, the duration of the blockade was 3.68 ± 0.09 h, whereas, in Group R, it was 2.26 ± 0.14 h, indicating a significant difference between the groups.

Conclusion: This study discovered that intravenous injection of 3 mL of 0.75% isobaric ropivacaine resulted in a delayed onset, sensory block (analgesia), and motor blockade for a short period compared to 3 mL of 0.5% hyperbaric bupivacaine.

Key words: Bupivacaine, Intrathecal, Ropivacaine

INTRODUCTION

In the current situation, surgery is moving quickly from being done on inpatients to outpatients. Therefore, traditional anesthetic techniques must be changed to fit the outpatient setting. Ambulatory anesthesia's primary goal is to expedite the healing process, resulting in a shorter hospital stay and fewer side effects. Furthermore, minimal side effects and rapid recovery after anesthesia are possible due to the availability of fast-acting anesthetics, analgesics, muscle relaxant drugs, and modern, sophisticated monitoring equipment.[1] In arthroscopic knee surgery, spinal anesthesia is gradually gaining ground on general anesthesia due to its lower post-operative morbidity and hospital stay.[2] Globally, the demand for rapid ambulation, rapid and complete recovery, and minimal side effects have increased after surgery.

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In contrast, regional anesthesia has gained global acceptance among anesthesiologists due to its numerous advantages.[3,4] For spinal anesthesia, bupivacaine has become the most common drug used. However, it has undesirable side effects, including bradycardia, hypotension, prolonged motor paralysis, neurotoxicity, and cardiotoxicity.[5-8] This led to the identification of pure S-enantiomer ropivacaine with a prolonged action mechanism.[9] Ropivacaine and bupivacaine are nearly identical in quality, onset, and sensory blockade duration. Still, ropivacaine produces a shorter duration of motor blockade and is safer.[3] This medication is beneficial for brief surgical and early recovery. This study compared the effectiveness and safety of ropivacaine and bupivacaine in the lower abdominal and lower limb surgeries. Using various adjuvant drugs and local anesthetic agents in conjunction with spinal anesthesia is a safe, reliable, and affordable technique that offers surgical anesthesia and prolonged relief from post-operative morbidity.

It provides a fast onset and sensory and motor blockade of pain and responses from the somatic, autonomic, and endocrine systems.[10] Epidural bupivacaine and etidocaine are frequently used in Cesarean section anesthesia in pregnant women, causing fatal cardiac toxicity. As a result, there is a need for pure selective, safe s enantiomer local anesthetics such as ropivacaine and levobupivacaine. Ropivacaine helps in safe ambulatory surgery due to its low incidence of transient neurological symptoms. It also can be an ideal alternative to lidocaine for this purpose.[11]

Bupivacaine is a long acting local anaesthetic agent of the amide type. However, hyperbaric bupivacaine achieves more effective sensory intrathecal anesthesia than glucose-free or plain bupivacaine, particularly when anesthesia is administered in the lateral position of patients.[11-14] However, the behavior of plain bupivacaine is often unpredictable, spreading to dermatomal levels of the cervical region. Large doses of intrathecal bupivacaine (IB) are frequently associated with extreme hypotension and delayed motor block recovery.[12] In contrast to bupivacaine and amide local anesthetic, ropivacaine is a long-acting agent with less penetration into massive myelinated motor fibers and low lipophilic than bupivacaine, resulting in a lower level of motor blockade. Due to its greater ability to differentiate between motor and sensory blocks, ropivacaine may be useful when the motor blockade is unpredictable. Central nervous system and cardiovascular toxicity are both less likely to occur due to the reduced lipophilicity feature.[13]

MATERIALS AND METHODS

The study was carried out at Government Villupuram Medical College and Hospital, Mundiyampakkam, after receiving approval from the Hospital Ethics Committee and signed informed consent from patients. This study enrolled 60 patients. They were between 18 and 75 years old and over 160 cm tall. Under spinal anesthesia, they underwent elective lower abdominal and lower limb surgeries. This prospective, randomized, and controlled study compared the onset, duration, hemodynamic stability, and side effects of the subarachnoid block between 0.5% bupivacaine hyperbaric and 0.755% ropivacaine isobaric. Patients who refused to participate, wanted to be rescheduled for emergency surgery, had a spinal anesthesia contradiction, had an allergy to amide local anesthetics, had a history of drug or alcohol abuse or were obese were excluded from the study.

Patients were randomly assigned to two groups. Group B was given 3 mL of % hyperbaric bupivacaine, while Group R was given 0.75% isobaric ropivacaine.

Patients were well instructed on the procedure of sensory or motor assessments before the start of the anesthetic procedure. Fifteen minutes before the surgical process, an intravenous line was demarcated after Ringer Lactate (500 mL) was given. The baseline blood pressure, heart rate, and oxygen saturation data were captured through non-invasive monitoring. Then, a 25 Quincke Babcock spinal needle was used to inject anesthetic into L3–L4 in the lateral position using a midline approach. The cerebral fluid was discovered to be clear and readily flowing, and analgesia was given at a rate of 0.2 mL/s. Blood pressure, heart rate, and oxygen saturation were checked on the patient following intrathecal anesthesia every 5 min for the remainder of the procedure, then every 10 min after that, and finally, every hour after that. We were alert and took care of adverse effects such as bradycardia, nausea, and vomiting.

After the T6 or higher dermatome was blocked, the surgery could begin. First, a sensory blockade was tested using a hypodermic needle every 10 min until full recovery was achieved, then every 5 min until loss of sensation was detected. Next, we evaluated motor blockades using a modified Bromage scale.

In this study, the Bromage score of 3 and the intrathecal administration time interval are used to determine the onset time of motor blockade [Table 1].

When referring to the duration of a sensory or motor blockade, this term refers to the period beginning with the intrathecal administration of the drug and ending with the point at which the sensory blockade has been completely resolved or the point at which the Bromage score has returned to zero, whichever comes first.

The sensory blockade's maximum level of action, the onset, sensory and motor blockade duration, and the interval from the intrathecal route of administration to the point of a two-segment regression function were all recorded. The quality of intraoperative analgesia was graded as

1. Excellent (no discomfort or pain)
2. Good (pain or discomfort and no need for analgesia) borrowed
3. Fair (pain that required additional analgesics)
4. Poor (moderate or severe pain requiring 100 mcg fentanyl or general anesthesia). Patients were assessed for adverse effects such as headache, backache, and temporary neurological symptoms on surgical days 1 and 6.

Statistical Analysis

The analysis was performed using the statistical software SPSS. Continuous variables are given as median (IQR) or mean (standard deviation). Proportional variables are categorical variables. Continuous variables are compared for significance with the help of a *t*-test. The Chi-square test was used for categorical data. <0.05 *P*-value is considered significant.

RESULTS

We found no statistically significant difference between Group R and Group B in terms of gender, age, ASA grading, sensory level blockage hemodynamic parameters, such as heart rate, diastolic blood pressure, systolic blood pressure, respiratory rate, and mean arterial pressure. However, there are statistically significant differences between the two groups' onset, duration, and sensory and motor blockade regression. The onset of sensory blockade was fast in Group B (2.17 ± 0.26 min), whereas in Group R (6.76 ± 0.19 min), it was delayed. This difference in the onset of sensory blockade between Groups B and R was significant ($P < 0.0001$). About 93.3% of patients in Group R had a maximum sensory level of T6, compared to 83.3% in Group B. T4 levels were achieved in 16.6% of Group B patients and 6.7% of Group R patients [Table 2]. Regression of sensory blockade duration was greater in Group B (102 ± 10.88 min) while in it was half in Group R (58 ± 11.73 min); this difference was clinically significant ($P < 0.0001$). The onset of motor blockade onset is earlier in Group B, which was 2.42 ± 0.13 min, compared to Group R, which was 8.82 ± 0.11 min, with a clinically significant difference ($P < 0.0001$). The duration of analgesia refers to the length of the blockade, which was longer in Group B (3.68 ± 0.09 h) than in Group R (2.26 ± 0.14 h), indicating a significant ($P < 0.0001$) difference between the groups. The length of the blockade was longer in Group B than in Group R [Table 3].

Table 1: Modified Bromage scale for motor blockade assessment

Grade	Criteria	Degree of motor blockade
1	Movement of the feet and legs	0% (Nil)
2	Only able to bend knees with little restriction on foot movement	33% (partial)
3	Having unrestricted movement in the feet yet unable to bend the knees	66% (almost complete)
4	Unable to move legs or feet	100% (complete)

DISCUSSION

A subarachnoid block is a well-regarded effective anesthetic method with a high success rate and a decent safety profile. As a result, research is still ongoing to find an appropriate medicine that is inexpensive and effective and has minimum side effects while also speeding up the recovery of patients. New local anesthetics are being developed in this approach, with the primary goal of improving the condition of patients. In addition, the medicine should act quickly and without side effects, allowing patients to be discharged sooner. Due to this, we decided to compare ropivacaine's effectiveness to bupivacaine, the most often prescribed and well-established anesthetic.

Mantouvalou *et al.*[10] discovered a greater cephalad spread of sensory blocks with bupivacaine compared to 15 mg of intrathecal isobaric ropivacaine and 10 mg of bupivacaine during the resection of the prostate, which is consistent with our study group's findings. A double-blind and randomized controlled trial by Chari *et al.* found that levobupivacaine's motor block onset was nearly the same in both groups. In contrast, the bupivacaine group's onset was significantly faster and more effective than the ropivacaine group ($P < 0.05$).[14]

Similarly, other comparative studies found that ropivacaine produces delayed onset compared to bupivacaine.[10,15] In

Table 2: Level of sensory blockade among participants

Group	T4	T6	Total	Chi-square	*P*-value
Group B	5	25	30	1.45	0.22
Group R	2	28	30		
Total	22	38	60		

Table 3: Blockade among participants

Blockade	Group B	Group R	*P*-value
Time of onset of sensory blockade	2.17±0.26	6.76±0.19	0.0001
Regression of sensory blockade to l1	102±10.88	58±11.73	0.0001
Time of onset of motor blockade	2.42±0.13	8.84±0.11	0.0001
Duration of motor blockade	3.68±0.09	2.26±0.14	0.0001

the present study, Group B experienced sensory blocking in 2.17 min, whereas Group R experienced it in 6.76 min. According to hemodynamic measurements, there was no significant difference across groups. In Group R, 93.3% of patients had a maximum sensory level of T6, compared to 83.3% in Group B. T4 levels were achieved in 16.6% of Group B patients and 6.7% of Group R patients. The level of sensory blockade was enough in both groups, which was consistent with a finding of the Bhat and Upadya study.[16]

The time for regression of sensory blockade is more in Group B (102 ± 10.88 min) compared to Group R (58 ± 11.73 min). Similarly, when Arish Sadaf and his colleagues studied 70 patients separated into two groups for their comparative and observational study, Group R received ropivacaine (0.75%) + Fentanyl 25 μg (0.5 mL). Group B received bupivacaine (0.5%) + Fentanyl 25 μg (0.5 mL). There was a statistically significant regression in sensory blockage in the group given ropivacaine, which had $P < 0.001$ value, while the group receiving bupivacaine had no such regression.[17]

Intrathecal ropivacaine (IR) and IB were examined in a study by Sanchez and colleagues in 2009. Although they observed a significant difference in the length of a blockade in the groups $P < 0.001$, the IB Group (266.5 ± 29.5) had a longer period of a blockade than the IR Groups (226.4 ± 22.3 min).[18] We discovered that Group B's blockade lasted an average of 3.68 ± 0.09 h. In contrast, Group R's lasted for an average of 2.26 ± 0.14 h, indicating a significant difference between Group R and Group B.

CONCLUSION

Compared to 0.5% hyperbaric bupivacaine, 0.75% isobaric ropivacaine administered in an equal volume of 3 mL resulted in a delayed onset, sensory block (analgesia), and motor blockade for a brief period. Hemodynamic measurements did not show any difference between the groups. Therefore, ropivacaine is a safer option than bupivacaine for the surgeries of perineal, lower abdominal, and lower limbs due to its lower incidence of adverse effects such as neurotoxicity and cardiovascular, as well as provide motor blockade for a short duration.

Limitations

The sample size should be increased to improve generalization. This study had only 60 participants divided into two groups. In addition, this study did not consider the basicity of local anesthetic, which is an important factor responsible for the peak height of sensory anesthesia.

REFERENCES

1. Shetty A, Raveendra US. Anaesthesia for daycare surgery. Nitte Univ J Health Sci 2015;5:97-103.
2. Jankowski CJ, Hebl JR, Stuart MJ, Rock MG, Pagnano MW, Beighley CM, *et al*. A comparison of psoas compartment block and spinal and general anaesthesia for outpatient knee arthroscopy. Anesth Analg 2003;97:1003-9.
3. McConachie I, McGeachie J, Barrie J. Regional anaesthetic techniques. In: Thomas EJ, Knight PR, editors. Wylie and Churchill Davidson's-A Practice of Anesthesia. Vol. 37. London: Arnold; 2003. p. 599-612.
4. Atkinson RS, Rushman GB, Davies NJ. Spinal analgesia: Intradural and extradural. In: Lee's Synopsis of Anaesthesia. Oxford: Butterworfh Heinemann; 1998. p. 691-716.
5. Hodgson PS, Neal JM, Pollock JE, Liu SS. The neurotoxicity of drugs given intrathecally (spinal). Anesth Analg 1999;88:797-809.
6. Barash PG, Cullen BF, Stoelting RK, editors. Clinical Anaesthesia. Philadelphia, PA: Lippincott Williams and Wilkins; 2001. p. 451-66.
7. Hiller A, Rosenberg PH. Transient neurological symptoms after spinal anaesthesia with 4% mepivacaine and 0.5% bupivacaine. Br J Anaesth 1997;79:301-5.
8. Hampl KF, Schneider MC, Drasner K. Toxicity of local spinal anaesthetics. Curr Opin Anaesthesiol 1999;12:559-64.
9. Ruetsch YA, Böni T, Borgeat A. From cocaine to ropivacaine: The history of local anaesthetic drugs. Curr Top Med Chem 2001;1:175-82.
10. Mantouvalou M, Ralli S, Arnaoutoglou H, Tziris G, Papadopoulos G. Spinal anaesthesia: Comparison of plain ropivacaine, bupivacaine and levobupivacaine for lower abdominal surgery. Acta Anaesth Belg 2008;59:65-7.
11. Luck JF, Fettes PD, Wildsmith JA. Spinal anaesthesia for elective surgery: A comparison of hyperbaric solutions of racemic bupivacaine, levobupivacaine, and ropivacaine. Br J Anaesth 2008;101:705-10.
12. Hallworth SP, Fernando R, Columb MO, Stocks GM. The effect of posture and Baricity on the spread of intrathecal bupivacaine for elective Cesarean delivery. Anesth Analg 2005;100:1159-65.
13. McClellan KJ, Faulds D. Ropivacaine: An update of its use in regional anaesthesia. Drugs 2000;60:1065-93.
14. Chari VR, Goyal A, Sengar P, Wani N. Comparison between intrathecal isobaric ropivacaine 0.75% with hyperbaric bupivacaine 0.5%: A double-blind, randomized controlled study. Anaesth Pain Intensive Care 2013;17:261-6.
15. Nalini A, Kuragayala U, Bhimeswar MV. A comparative study of intrathecal 0.5% isobaric ropivacaine in lower abdominal surgeries vs 0.5% isobaric bupivacaine. Int J Contemp Med Res 2016;3:77-83.
16. Bhat SN, Upadya M. Comparison of efficacy and safety of ropivacaine with bupivacaine for intrathecal anaesthesia for lower abdominal and lower limb surgeries. Anaesth Essays Res 2013;7:381.
17. Sadaf A, Patel JB, Desai JB, Chauhan D. Comparison of intrathecal 0.75% ropivacaine-fentanyl and 0.5% bupivacaine-fentanyl in equipotent doses for lower abdominal and lower limb surgeries under spinal anesthesia. Indian J Anesth Analg 2020;7:912.
18. Hinojosa-Sánchez O, Alamilla-Beltrán I, Han-Alonso R, Solano-Moreno H, Álvarez-Villaseñor AS, Ramírez-Contreras JP, *et al*. Subarachnoid blockade with ropivacaine versus bupivacaine in urologic and orthopaedic surgery. Rev Méd Inst Mex Seguro Soc 2009;47:539-44.

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Original Article

Determination of Pregnancy Outcome in High-Risk Cases of Placenta Previa in Tertiary Care Center

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Abstract

Background: Placenta previa is the life-threatening complication which endangers both maternal and fetal life; it is one of the obstetric complications which alter the health indicators of any institution. With the increase in cesarean rate, there is an increase in the incidence of placenta previa and the obstetric complications there on. Furthermore, in rural districts, where there is increased incidence of infection resulting in pelvic inflammatory disease and increased abortions result in increased incidence of placenta previa. Placenta previa is complete or partial depending on its relation to the internal os of the cervix with the placenta. It is a major risk factor for antepartum and postpartum hemorrhage. It can lead to renal failure, DIC, and MODS when associated with other complications or when diagnosed or managed late. In the past decade, it has contributed to major risk for hemorrhagic cause of maternal death. The presence of placenta previa would increase a woman's risk for placenta accreta spectrum (PAS). Uncontrolled postpartum hemorrhage from placenta previa or PAS may need multiple blood transfusion, *in situ* hysterectomy, admission to the intensive care unit, or even mortality, thereby ending the reproductive career. The incidence of placenta previa is 3–5/1000 pregnancies worldwide. Assisted reproductive technology and maternal smoking or tobacco consumption increases the risk of placenta previa. It highlights the role of an interprofessional team in managing patients with this condition to improve outcomes for mother and neonate.

Aims: This prospective study was conducted in the CEMONC center of Government Sivagangai Medical College, tertiary care center catering to three districts: (1) To analyze the common risk factors of placenta previa in rural set up, (2) role of serial monitoring, early admission and intervention in modifying maternal and fetal outcome, and (3) effectiveness of the intervention in reducing maternal and fetal mortality.

Materials and Methods: This prospective study was conducted in the Department of Obstetrics and Gynecology, Government Sivagangai Medical College from October 2021 to October 2022. Targeted populations for this study were all women diagnosed with placenta previa transabdominally either during the second and third trimesters of pregnancy or intraoperatively. Data were carefully extracted from medical records, reviewed, and analyzed. Inclusion criteria was placenta previa diagnosed preoperatively or intraoperatively. Exclusion criteria were patients with placenta located in upper segment, cases of bleeding per vaginum with abruptio placenta, bleeding per vagina due to local causes, and vesicular mole.

Statistical Analysis: Statistical analysis was done with SPSS, version 25.0. Categorical variables were expressed as number of cases and percentages (%).

Results: Pregnancies complicated by placenta previa were 41. Total delivery in that period was 5267. The magnitude of placenta previa was 0.78%. About 41.46% women were above 28 years of age and 70% were multigravidas. About 39.01% had major degree placenta previa, 51.2% had prior cesarean deliveries, 4.88% had prior abortion, and 56.09% preterm deliveries. About 100% cases delivered by cesarean delivery, 68.3% cases had postpartum hemorrhage and 9.76% had adherent placenta.

Conclusion: This study showed that the magnitude of placenta previa was 7 in 1000 pregnancies. Advanced maternal age, multiparity, and previous cesarean section were significantly associated risk factors of placenta previa. Adverse maternal outcomes due to placenta previa were postpartum hemorrhage, anemia, and also the need for blood transfusion due to significant amount of blood loss due to the disease condition and its complications. Neonates born to women with placenta previa were also at risk of being born preterm, intrauterine growth restriction, and respiratory distress syndrome. Hence, the detection of placenta previa should be encouraged and careful evaluation with timely delivery to reduce the associated maternal and perinatal complications is recommended.

Key words: Adherent placenta, Maternal morbidity, Placenta previa, Postpartum hemorrhage, Prior cesarean delivery

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INTRODUCTION

Placenta previa is the life-threatening complication which endangers both maternal and fetal life; it is one of the obstetric complications which alter the health indicators of any institution. With the increase in cesarean rate, there is an increase in the incidence of placenta previa and the obstetric complications there on. Furthermore, in rural districts, where there is increased incidence of infection resulting in pelvic inflammatory disease and increased abortions result in increased incidence of placenta previa. Placenta previa is complete or partial depending on its relation to the internal os of the cervix with the placenta.[1-3] Its a major risk factor for antepartum and postpartum hemorrhage. It can lead to renal failure, DIC, and MODS when associated with other complications or when diagnosed or managed late. In the past decade, it has contributed to major risk for hemorrhagic cause of maternal death.[4] The presence of placenta previa would increase a woman's risk for placenta accreta spectrum (PAS).[5] Uncontrolled postpartum hemorrhage from placenta previa or PAS may need multiple blood transfusion, *in situ* hysterectomy, admission to the intensive care unit, or even mortality, thereby ending the reproductive career. The incidence of placenta previa is 3–5/1000 pregnancies worldwide. Assisted reproductive technology and maternal smoking or tobacco consumption increase the risk of placenta previa.[7]

The mid pregnancy routine fetal anomaly scan should include placental localization, thereby identifying women at risk of persisting placenta previa or a low-lying placenta.

For pregnancies at more than 16 weeks of gestation, the term low-lying placenta should be used when the placental edge is <20 mm from the internal os on transabdominal or transvaginal scanning (TVS).

If the placenta is thought to be low lying (<20 mm from the internal os) or previa (covering the os) at the routine fetal anomaly scan, a follow-up ultrasound examination including a TVS is recommended at 32 weeks of gestation to diagnose persistent low-lying placenta and/or placenta previa.

In women with a persistent low-lying placenta or placenta previa at 32 weeks of gestation who remain asymptomatic, an additional TVS is recommended at around 36 weeks of gestation to inform discussion about mode of delivery. Cervical length measurement may help facilitate management decisions in asymptomatic women with placenta previa. A short cervical length on TVS before 34 weeks of gestation increases the risk of preterm emergency delivery and massive hemorrhage at cesarean section. Plan antenatal care, including hospitalization, to individual woman's needs and social circumstances, for example, distance between home and hospital and availability of transportation, previous bleeding episodes, hematology laboratory results, and acceptance of receiving donor blood or blood products. A single course of antenatal corticosteroid therapy is recommended between 34 + 0 and 35 + 6 weeks of gestation for pregnant women with a low-lying placenta or placenta previa and is appropriate before 34 + 0 weeks of gestation in women at higher risk of preterm birth. Neonates born to mothers with placenta previa more likely suffer from preterm birth, perinatal death, congenital malformations, and Apgar scores at 1 min and 5 min lower than 7.[5-11] Perinatal morbidity is also studied that majority of babies require resuscitation and neonatal intensive care unit (NICU) admission.[8] Moreover, the most substantial outcome of this disorder is small for gestational age and low birth weight.[9,10] The complication of placenta previa is limited not only to the antepartum period but also to the intrapartum and postpartum courses which were complicated with a high rate of cesarean delivery, peripartum cesarean hysterectomy, morbid adherent of placenta, and postpartum hemorrhage.[6] Pregnancies complicated with placenta previa also have a significantly higher rate of postpartum anemia and delayed discharge from the hospital.

Aim of the Study

This prospective study was conducted in the CEMONC center of Government Sivagangai Medical College, tertiary care center catering to three districts.

1. To analyze the common risk factors of placenta previa in rural set up
2. Role of serial monitoring, early admission, and intervention in modifying maternal and fetal outcome
3. Effectiveness of the intervention in reducing maternal and fetal mortality.

MATERIALS AND METHODS

The study was conducted in Government Sivagangai Medical College and Hospital. The data were collected from October 2021 to October 2022.

Sample Size

All pregnant women with placenta previa diagnosed sonologically or presented with bleeding per vaginum due to placenta previa was considered for this study. First, all cases were identified from health management information system, and their medical registration number was used to access patient's information. Complete birth registry records were taken for analysis. From 5267 deliveries, 41 cases of placenta previa were identified.

Inclusion and Exclusion Criteria

Inclusion criteria

All singleton pregnancies diagnosed with placenta previa transvaginally or transabdominally either during the second and third trimesters of pregnancy or intraoperatively were include in the study.

Exclusion criteria

The following criteria were excluded from the study:

1. Cases of bleeding per vaginum with abruptio placenta
2. Bleeding per vagina due to local causes, vesicular mole
3. All singleton pregnancies without placenta previa.

Study Variables

Independent variables

i. Sociodemographic factors
ii. Obstetric factors
iii. Neonatal and maternal complications.

Dependent variables

i. Placenta previa

Data collection tools, a checklist, were designed to collect data about patients sociodemographic characteristics, obstetric and gynecological history, mode of delivery, and maternal and neonatal outcome and complications data quality management. Data were checked for completeness and consistency before data entry by the principal investigator; the completed questionnaire was coded. For data cleaning, the coded data were entered into EPI Info version 3.5.

Data Analysis and Processing

Data were entered into EPI Info version 3.5.1 for data exploration and cleaning. The cleaned data were exported to SPSS version 25 for statistical analysis that descriptive statistics was used to summarize categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

The following data were obtained from the present study. The total number of deliveries occurred from October 2021 to October 2022 was 5267. Out of that, 41 cases were placenta previa; hence, magnitude of placenta previa was 0.78%.

Based on Table 1, where sociodemographic factors were analyzed, it is noted that incidence of placenta previa is more in <30 years, about 75.6%.

The mean age was 28 years. Almost 97.56% patients had antenatal check-up, only one patient was unbooked.

Based on this study [Table 2], it is noted that about 70% patients were multiparous, which signifies that previous disruption of endometrial and myometrial tissues contribute to higher incidence.[11] In this series, as multiparous constitutes as majority, 51.22% had previous history of cesarean, 4.88% patients had history of abortions. About half of the cases tend to deliver preterm, 46.34% of cases were <36 weeks, 34.14% cases were late preterm, and only 19.51% constitutes term delivery. Almost all cases were delivered by cesarean. About 73.17% of cases were done as emergency procedure, where the patient has come with either bleeding or in labor which necessitates immediate intervention.

Type of placenta previa depends on the location that was noted either by ultrasound diagnosis of previa or noted during cesarean delivery for some other indication and where ultrasound examination had failed to notice placenta previa which is shown in Table 3. There were 16 (39.01%) cases of major degree placenta previa in the present series.

Table 1: Sociodemographic characteristics

Sociodemographic parameters	Total	Percentage
Age		
<25 years	14	34.14
25–30 years	17	41.46
31–35 years	9	21.95
36–40 years	1	2.43
Antenatal follow up		
Yes	40	97.56
No	1	2.44

Table 2: Obstetric characteristics

Obstetric parameters	Total	Percentage
Obstetric code		
PRIMI	12	29.26
Multi	29	70.74
Gestational age		
<36 weeks	19	46.34
36–36 weeks 6 days	14	34.14
>37 weeks	8	19.51
Mode of delivery		
LSCS	41	100
Vaginal delivery	0	0
Procedure		
Elective cesarean	11	26.83
Emergency cesarean	30	73.17
Type of anesthesia		
Spinal anesthesia	36	87.80
General anesthesia	5	12.20
Previous obstetric history		
Previous LSCS	21	51.22
Hysterectomy	1	2.44
Abortion	2	4.88

Table 4 depicts maternal complications associated with placenta previa. In this series, 68.23% of patients had postpartum hemorrhage which is one of the dreadly complication in obstetrics as it results in maternal morbidity and mortality. About 85.37% of patient required blood transfusion during delivery in view of placenta previa. Majority of the patient had postpartum anemia in spite of blood transfusion which required further correction during postnatal period which constituted about 75.61%. One of the recent innovations was SR cannula usage whose mechanism of action is decreasing blood loss by creating negative pressure inside the uterine cavity, thus assisting constriction of spiral arterioles by normal physiological myometrial contraction and thus preventing hysterectomy. In this series, we used SR cannula in about 51.21% patients along with bilateral uterine artery ligation. Thus, hysterectomy was on; y 14.63% in our institution and also prevented maternal mortality. About 14.63% patient underwent hysterectomy in view of placenta accreta syndrome. Due to complications, duration of hospital was slightly increased when compared with other conditions which constitute about 46.34%. Adjacent visceral injury that is bladder injury was about 4.87% which was associated with the previous history of cesarean. In this series,as shown in Table 5.

Table 3: Location of placenta

Location of placenta	Total	Percentage
Type I	5	12.20
Type IIA	12	29.27
Type IIB	9	21.95
Type III	8	19.51
Type IV	8	19.5

Table 4: Maternal complications

Parameters	Total	Percentage
PPH	28	68.23
Adherent placenta	4	9.76
Blood transfusion	35	85.37
Hysterectomy	6	14.63
Post-partum ANEMIA	31	75.61
SR cannula usage	21	51.21
Surgical site infection	5	12.20
Bladder injury	2	4.87
Duration of hospital stay		
10 days	22	53.66
>10 days	19	46.34

Table 5: Neonatal outcome

Neonatal parameters	Total	Percentage
Birth weight		
<1.5 kg	4	9.76
1.6–2 kg	4	9.76
2–2.5 kg	21	51.22
>2.5 kg	12	29.27
IUD	1	2.44
APGAR at birth		
<6	14	34.14
>6	27	65.85
PRE term	19	46.34
Late PRE term	14	34.14
Term	8	19.51
NICU admission	23	56.09
Preterm care	16	39.02
RDS	7	17.07
Neonatal death	4	9.76

In this series, as preterm delivery was more in placenta previa, NICU admission contributed to 56.09%. Among total NICU admission, 39.02% required preterm care, 17.07% babies had respiratory distress syndrome, and 2.44% were intrauterine death due to placenta previa bleeding. About 51.22% constitutes low birth weight due to prematurity and IUGR. In this series, 65.85% babies had Apgar score above 6 at birth. Neonatal death occurred due to prematurity which constitutes about 9.76%.

DISCUSSION

Placenta previa is one of the dreadly complication in obstetrics as it leads to maternal and neonatal morbidity and mortality. Placenta previa affects 0.3–2% of pregnancies in the third trimester and has become more evident secondary to the increasing trends of cesarean sections.[11] In this study, magnitude of placenta previa was 0.78%. The risk factors correlating with placenta previa are advanced maternal age, multiparity, tobacco use, prior suction, and curettage, assisted reproductive technology, history of cesarean section(s), and prior placenta previa.[3] Similarly, in this study, the previous cesarean contributed to about 51.22% and multiparity constituted about 70.74%. These results are comparable with the study done by Ojha *et al.*, Wu *et al.*[16,17] The relationship between advanced maternal age and placenta previa may be confounded by higher parity and a higher probability of previous uterine procedures or fertility treatment. However, it may also represent an altered hormonal or implantation environment.[12] Painless vaginal bleeding during the second or third trimester of pregnancy is the usual presentation. The bleeding may be provoked from intercourse, vaginal examinations, labor, and at times, there may be no identifiable cause.[13] On speculum examination, there may be minimal bleeding to active bleeding. With the diagnosis of placenta previa, the patient is scheduled for elective delivery at 36–37 weeks through cesarean section.[14,15] However, some patients with placenta previa present with complications and require urgent cesarean sections at an earlier gestational

age. Patients with excessive or continuous vaginal bleeding should be delivered through cesarean section regardless of gestational age. If bleeding subsides, then expectant management is permissible if the gestational age is <36 weeks. If at or >36 weeks of gestation, then cesarean delivery is recommended.[15] The patient should be admitted and, if qualified, receive magnesium sulfate for fetal neuroprotection and steroids for fetal lung maturity. Inpatient versus outpatient management depends on the stability of the patient, the number of episodes of bleeding, proximity to the hospital, as well as compliance. A vertical skin incision is the recommended incision for optimal exposure. A high vertical uterine incision may be required if the placenta is covering the lower uterine segment, or if the lower uterine segment is underdeveloped. After delivery of the fetus, the placenta spontaneously detaches, and the uterine incision can be closed. There may be hemorrhage after detachment of the placenta secondary to the decreased contractibility of the lower uterine segment, which can be managed with bimanual uterine massage, uterotonics, B-Lynch sutures, Cho sutures, uterine artery, or internal iliac artery ligation.[4,19] As NHM Tamil Nadu recommends SR Cannula, a recent innovation to control postpartum hemorrhage, in this study, it was used in about 51.4% of cases along with uterine artery ligation. At times, the massive hemorrhage may not be controlled with conservative measures, and a hysterectomy is necessary.[4] If the placenta does not detach or partially detaches then the patient has PAS, and the placenta should remain *in situ*, the uterine incision closed, and a cesarean hysterectomy should follow.[7,10] In this study, PAS constituted about 9.76%, hence proceeded to placenta *in situ* hysterectomy. If there is high suspicion for PAS, then a cesarean section should be performed without manipulation of the placenta. There is a three-fold to four-fold increased neonatal mortality and morbidity rate with placenta previa primarily from preterm delivery. The neonate is at increased risk of preterm birth, lower birth weight, lower APGAR scores, and increased risk for respiratory distress syndrome. In this study, preterm delivery constituted 80.49%. This is also supported by the studies done by Rosenberg *et al.* and Faiz *et al*.[17-19]

CONCLUSION AND RECOMMENDATION

This study showed that the magnitude of placenta previa was 7 in 1000 pregnancies. Advanced maternal age, multiparity, and previous cesarean section were significantly associated risk factors of placenta previa. Adverse maternal outcomes due to placenta previa were postpartum hemorrhage, anemia, and also the need for blood transfusion due to significant amount of blood loss due to the disease condition and its complications. Neonates born to women with placenta previa were also at risk of being born preterm, intrauterine growth restriction, and respiratory distress syndrome. Hence, the detection of placenta previa should be encouraged and careful evaluation with timely delivery to reduce the associated maternal and perinatal complications is recommended. Patients with placenta previa should be considered as high-risk antenatal mother and compatible blood should always be available for such cases before considering surgical mode of delivery that is cesarean. Family welfare services should also be insisted as a strategy toward in reduction of parity, cesarean section rate, and thereby the incidence of placenta previa. Strategies and protocols should be emphasized to reduce the rate of cesarean section, senior doctors and interdisciplinary team have to be involved in the management of all cases of placenta previa.

REFERENCES

1. Ahn KH, Lee EH, Cho GJ, Hong SC, Oh MJ, Kim HJ. Anterior placenta previa in the mid-trimester of pregnancy as a risk factor for neonatal respiratory distress syndrome. PLoS One 2018;13:e0207061.
2. Wang Y, Hu C, Pan N, Chen C, Wu R. Prophylactic uterine artery embolization in second-trimester pregnancy termination with complete placenta previa. J Int Med Res 2019;47:345-52.
3. Martinelli KG, Garcia ÉM, Neto ET, Gama SG. Advanced maternal age and its association with placenta praevia and placental abruption: A meta-analysis. Cad Saude Publica 2018;34:e00206116.
4. Ryu JM, Choi YS, Bae JY. Bleeding control using intrauterine continuous running suture during Cesarean section in pregnant women with placenta previa. Arch Gynecol Obstet 2019;299:135-9.
5. Silver RM, Branch DW. Placenta accreta spectrum. N Engl J Med 2018;378:1529-36.
6. Adere A, Mulu A, Temesgen F. Neonatal and Maternal complications of placenta praevia and its risk factors in Tikur Anbessa specialized and Gandhi memorial hospitals: Unmatched case-control study. J Pregnancy 2020;2020:5630296.
7. Jauniaux E, Alfirevic Z, Bhide AG, Belfort MA, Burton GJ, Collins SL, *et al*. Placenta praevia and placenta accreta: Diagnosis and management: Green-top Guideline No. 27a. BJOG 2019;126:e1-48.
8. Prasanth S, Mehta P, Rajeshwari KS. Maternal and fetal outcome of placenta previa in a tertiary care institute: A prospective two year study. Indian J Obstet Gynecol Res 2016;3:274-8.
9. Gargari SS, Seify Z, Haghighi L, Shariati MK, Mirzamoradi M. Risk factors and consequent outcomes of placenta previa: Report from a referral center. Acta Med Iran 2016;54:713-7.
10. Kassem GA, Alzahrani A. Maternal and neonatal outcomes of placenta previa and placenta accreta: Three years of experience with a two-consultant approach. Int J Womens Health 2013;5:803-10.
11. Silver RM. Abnormal placentation: Placenta previa, vasa previa, and placenta accreta. Obstet Gynecol 2015;126:654-68.
12. Carusi DA. The placenta accreta spectrum: Epidemiology and risk factors. Clin Obstet Gynecol 2018;61:733-42.
13. Pedigo R. First trimester pregnancy emergencies: Recognition and management. Emerg Med Pract 2019;21:1-20.
14. Feng Y, Li XY, Xiao J, Li W, Liu J, Zeng X, *et al*. Risk factors and pregnancy outcomes: Complete versus incomplete placenta previa in mid-pregnancy. Curr Med Sci 2018;38:597-601.
15. ACOG committee opinion No. 764: Medically indicated late-preterm and early-term deliveries. Obstet Gynecol 2019;133:e151-5.
16. Ojha N. Obstetric factors and pregnancy outcome in placenta previa. J Inst Med 2012;34:38-41.

17. Wu S, Kocherginsky M, Hibbard J. Abnormal placentation: twenty-year analysis. Am J Obstet Gynecol 2005;192:1458-61.
18. Rosenberg T, Pariente G, Sergienko R, Wiznitzer A, Sheiner W. Critical analysis of risk factors and outcome in placenta previa. Arch Gynecol Obstet 2011;284:47-51.
19. Faiz AS, Ananth CV. Etiology and risk factors for placenta previa: An overview and meta-analysis of observational studies. J Matern Fetal Neonatal Med 2003;13:175-90.

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Original Article

Cytological Evaluation of Cervical PAP Smears in a Tertiary Care Center

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Abstract

Background: Cervical carcinoma is the leading cause of death among women. Infections are the common gynecological problems and are curable. Screening tests are used for the detection of an infection, precancerous, and cancerous lesions. Conventional Papanicolaou (PAP) test is commonly used for early diagnosis and follow-up.

Aims and Objectives: The objectives of the study are as follows: (1) To study the cervical cytology in all age groups. (2) To evaluate the PAP smear according to Bethesda system

Materials and Methods: The prospective study was conducted and total of 815 PAP smears were evaluated in the department of pathology, Santhiram Medical College and General Hospital, Nandyal, Andhra Pradesh, during the period of 6 months from January 2022 to June 2022.

Results: Out of 815 cases, 795 (97.5%) cases were satisfactory and 20 cases (2.5%) were non satisfactory. Among 795 cases, 256 (32.2%) cases with negative for intraepithelial lesions or malignancy, 462 (58.1%) cases with inflammatory lesions, 33 (4.2%) cases with atypical squamous cells with undetermined significance, 20 (2.5%) cases with low-grade squamous intraepithelial lesion, and 12 (1.5%) cases with high-grade squamous intraepithelial lesion. 4 (0.5%) cases with atypical glandular cells of undetermined significance and 8 (1%) cases with squamous cell carcinoma.

Conclusion: Cervical cytological PAP test is used a screening test for detection of inflammatory, pre-cancerous, and cancerous lesions.

Key words: High-grade squamous intraepithelial lesion, Low-grade squamous intraepithelial lesion, Papanicolaou test, Squamous cell carcinoma

INTRODUCTION

Carcinoma cervix is the fourth leading cause of morbidity and mortality in developing countries. Cervical carcinoma is preventable and curable cancer as the precancerous cells are found in early stage of disease.[1]

The strategy of WHO is to reduce the incidence of cervical cancer by increasing the awareness of Papanicolaou (PAP) screening tests. PAP test is very specific, simple, rapid, and cost-effective. PAP smear test is ideal for mass screening programs and useful to evaluate the various cellular alterations of cervical abnormalities.

The present study was done to study the cervical PAP smears to classify the smears as inflammatory, pre-malignant, and malignant lesions.

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MATERIALS AND METHODS

The prospective study was conducted in the Department of Pathology at Santhiram Medical College and General Hospital, Nandyal, from January 2022 to June 2022. Samples were collected from all women of 20–70 years. The

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study was conducted for a period of 6 months. PAP smears are received from the OBG and gynecology department. Smears are stained with PAP staining. Patients details were obtained from requisition and case sheets.

Inclusion Criteria

Women in the age group of 20–70 years with history of leucorrhea, foul smelling discharge, and unhealthy cervix were included in the study.

Exclusion Criteria

Women with theprevious surgical procedures on the cervix, unmarried females, pregnant women, and known case of carcinoma cervix are excluded from the study. Ethical approval was taken from the Institutional Ethical Committee.

Cervical PAP smears reporting were done according to Bethesda system (2014).

Bethesda System for Reporting PAP Smears

Specimen adequacy

1. Satisfactory for evaluation
2. Unsatisfactory for evaluation (Hemorrhage, severe inflammation).

General categorization

1. Negative for intraepithelial lesion or malignancy (NILM)
2. Epithelial cell abnormalities
3. Others.

Non-neoplastic results, organisms

1. *Trichomonas vaginalis*
2. Fungal organisms morphologically consistent with *Candida* species
3. Shift in flora suggestive of Bacterial vaginosis
4. Bacteria morphologically consistent with actinomyces species
5. Cellular changes consistent with herpes simplex virus infection.

Other neoplastic findings

1. Reactive cellular changes due to infection
2. Reactive cellular changes due to radiation
3. Reactive cellular changes due to intrauterine device
4. Benign glandular cells after hysterectomy
5. Atrophy.

Epithelial cell abnormalities

1. Squamous cell abnormalities
   a. Atypical squamous cell undetermined significance (ASC-US)
   b. ASC cannot exclude (ASC-H) high grade squamous intraepithelial lesion (HSIL).
2. Low-grade squamous intraepithelial lesion (LSIL)
3. HSIL
4. Squamous cell carcinoma (SCC).

Glandular cell abnormalities

1. Atypical glandular cells (specify endocervical, endometrial, or not otherwise specified)
2. Atypical glandular cells favor neoplastic (specify endocervical or not otherwise specified)
3. Endocervical adenocarcinoma *in situ*
4. Adenocarcinoma (specify endocervical, endometrial, extrauterine, or not otherwise specified).

RESULTS

In this study, out of 815 cases, the age range of the patient was 21–70 years. Maximum number of cases 304 (38.2%) were in the age group of 41–50 years. Second highest 256 cases (32.2%) were seen in between 31 and 40 years and least number of cases 64 (5.6%) were seen in 60–70 years [Table 1].

In the present study, 20 (2.5%) smears were unsatisfactory and 795 (97.5%) smears were satisfactory and analyzed according to Bethesda system [Table 2].

Two hundred and fifty-six (32.2%) cases were in the category of NILM and inflammatory were 462 (58%) cases. In this study, the epithelial cell abnormalities were 77 (9.6%) among these, ASCUS 33 (4.2%), LSIL 20 (2.5%), SCC 8 cases (1%), HSIL 12 (1.5%), and AGUS 4 (0.5%) in the age group of 41–50 years. Out of eight cases of SCC, 4 cases (0.5%) were seen in the age group of 41–50 years and two cases(0.2%) were seen between 31 and 40 years [Tables 3-5 and Figures 1-4]. For all cases of SCC, cervical biopsies were histologically evaluated.

The clinical presentation was PV discharge in 613 (75.2%) patients, 408 patients had lower abdominal pain (50.1%),

Table 1: Age distribution

Age distribution	No of patients	Percentage
21–30	112	14.1
31–40	256	32.2
41–50	304	38.2
51–60	79	9.9
61–70		5.6
Total	795	100

Table 2: PAP smear sample adequacy

PAP smear	No of cases	Percentage
Satisfactory for evaluation	795	97.5
Unsatisfactory	20	2.5
Total	815	100

PAP: Papanicolaou

117 patients had genital itching (14.4%), 105 patients with irregular bleeding (12.9%), five patients had post coital bleeding (0.6%), and 102 patients with utero vaginal prolapse (12.5%) [Table 6]. Most of the patients had multiple symptoms and 150 (18.4%) patients had routine screening without any symptoms.

DISCUSSION

Carcinoma of cervix is the leading cause of death in Indian women.[2] PAP smear test is an effective mass screening program for early detection of precancerous conditions to reduce the morbidity and mortality rate.

During the study period, 815 smear were evaluated. Among 815 smear 20 (2.5%) were unsatisfactory. Our study differed with Bamanikar *et al.*[3] (5.7%) Ranabhat *et al.*[4] (3.12%), Sarma *et al.*[5] (6.6%) Alta *et al.*[6] (6.3%), Laxmi *et al.*[7] (4.36%) Vaghela *et al.*[8] (4.36%) and Renuka *et al.* (3.38%).[9] Our study correlated with Ramu *et al.* (2.01%).[10]

In our study, out of 795 cases (97.5%), 256 cases (32.2%) were negative for intraepithelial malignancy with normal PAP smear. The present study differed with Renuka *et al.* (97.4%),[9] Ranabhat *et al.* (98.25%),[4] Laxmi *et al.* (95.53%),[7] and Tailor *et al.* (98.10%).[11] Our study correlated with the studies done by Ramu *et al.* (35.88%).[10]

In our study, 462 cases (58.1%) were inflammatory smears such as non-specific 166 (21%), Bacterial vaginosis 185 (23.3%), *Candida vaginalis* 57 (7.2%), and *T. vaginalis* 54 (6.8%) [Table 7 and 8]. Bacterial vaginosis was most common cervical vaginal infection in the age group of 21–50 years and lowest was 50–70 years. Zubair *et al.* reported 307 cases (55.3%).[12] Our study differed with Zubair *et al.* Adad *et al.*[13] and Zubair *et al.* documented the frequency of *Candida* and *Trichomonas* as 22.5% and 3.4%, 2.9% and 2.3%, respectively our study differed with above author studies.

In the present study, the bacterial vaginosis (23.3%) was the most common cervical-vaginal infection. Our study differed with Renuka *et al.* (12.30%),[9] Ranabhat *et al.*,[4] Vaghela *et al.*,[8] Ramu *et al.*,[10] Saha *et al.*,[14] Verma *et al.*,[15] and Zubair *et al.*[12] as 7.6%, 1.6%, 0.72%, 7.1%, 8.8%, and 2.9%.

In the present study, the *Candida* infection was 7.2% and the study differed with Renuka *et al.* (1.86%),[9] Ranabhat *et al.* (1%),[4] Ramu *et al.*[10] 3.71%, and Tailor *et al.*[11] 0.45%.

Renuka *et al.*[9] 0.22% cases of *T. vaginalis* and other studies were 0.36%, 0.77%, 3.2%, and 0.6% cases. Our study differed with above author studies.

In the present study, 256 (32.2%) cases were NILM with normal PAP smears. Our study differed with study done by Ranabhat *et al.*,[4] Laxmi *et al.*,[7] and Tailor *et al.*[11] found as 98.29%,95.53%, and 98.10%. Vaghela *et al.*,[8] Ramu *et al.*,[10] and Saha *et al.*[14] as 47%, 35.88%, and 50.6%.

In the present study, ASCUS 33 (4.2%) was most common epithelial abnormality. Mulay *et al.*[16] and Patel *et al.*[17] documented the similar findings. Hence, our study correlated with above author studies. Tailor *et al.*[11] documented high incidence of ASCUS 40.7%. Our study revealed low incidence hence differed with above author study. Lahari and Bharathi 22 (4.4%)[18] and Zubair *et al.*[12] 18 (3.2%) documented the ASCUS cases. Our study correlated with above author studies.

Our study revealed the epithelial abnormalities as LSIL and HSIL in the age group of 20–70 years. Similar findings were documented by Ranabhat *et al.*,[4] Alta *et al.*,[6] and Patel *et al.*[17] In our study, LSIL and HSIL was 2.5% and 1.5%.

Table 3: PAP smear findings

PAP smear report	No of cases	Percentage
NILM	256	32.2
Inflammatory	462	58.1
Epithelial cell abnormality	77	9.7
Total	795	100

PAP: Papanicolaou, NILM: Negative for intraepithelial lesion or malignancy

Table 4: Case wise and age wise distribution of PAP smears

Cytological diagnosis	21–30	31–40	41–50	51–60	61–70	No of cases	Percentage
NILM	26	104	101	11	14	256	32.2
Inflammatory	84	141	171	46	20	462	58.1
ASCUS	1	3	13	12	4	33	4.2
LSIL	1	2	8	6	3	20	2.5
HSIL	0	4	5	2	1	12	1.5
AGUS	0	0	2	1	1	04	1
SCC	0	2	4	1	1	08	0.5
Total	112	256	304	79	44	795	100

LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, ASCUS: Atypical squamous cell undetermined significance, SCC: Squamous cell carcinoma

Table 5: Distribution of cases with epithelial cell abnormalities

Cytological diagnosis	No of cases (*n*=77)	Percentage	Over all percentage (*n*=795)
ASCUS	33	42.9	4.2
LSIL	20	26	2.5
HSIL	12	15.6	1.5
AGUS	04	5.2	0.5
SCC	08	10.3	1
Total	77	100	9.6

LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, SCC: Squamous cell carcinoma

Table 6: Distribution of symptoms

Chief complaints	No of cases	Percentage
PV discharge	613	75.2
Lower abdominal pain	408	50.1
Genital itching	117	14.4
Abnormal irregular PV bleeding	105	12.9
Post-coital bleeding	05	0.6
Uterovaginal prolapse	102	12.5

Table 7: Distribution of inflammatory lesions

Inflammatory lesions	No of cases (*n*=462)	Percentage	Over all percentage (*n*=795)
Non specific	166	35.9	20.9
Specific	296	64.1	37.2
Total	462	100	58.1

Table 8: Distribution of specific inflammatory lesions

Specific inflammatory lesion	No of cases (*n*=296)	Percentage	Overall percentage (*n*=795)
Bacterial vaginosis	185	62.5	23.2
Candida	57	19.3	7.2
Trichomonas vaginalis	54	18.2	6.8
Total	296	100	37.2

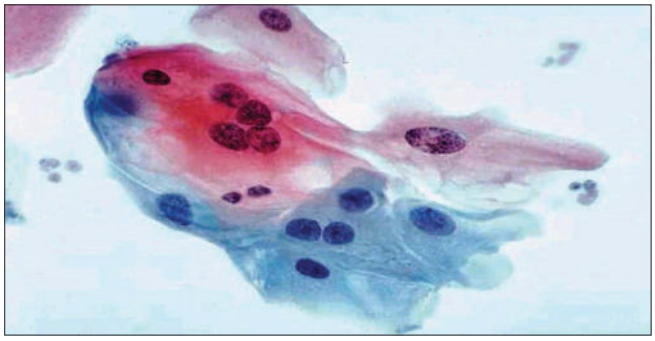

Figure 1: Ascus (400X) – atypical squamous cells of undetermined significance

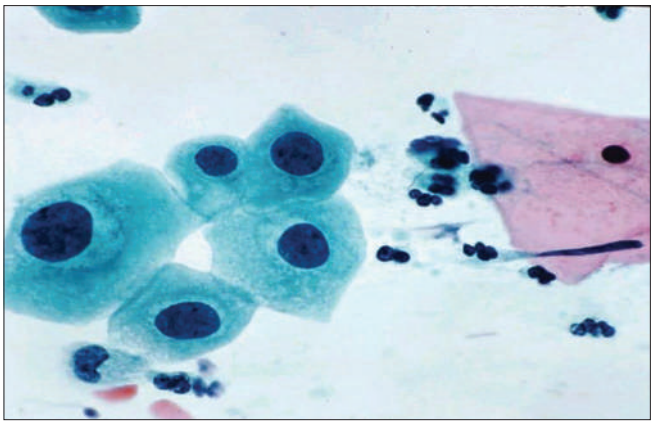

Figure 2: Lsil (400X) - low grade squamous intraepithelial lesion

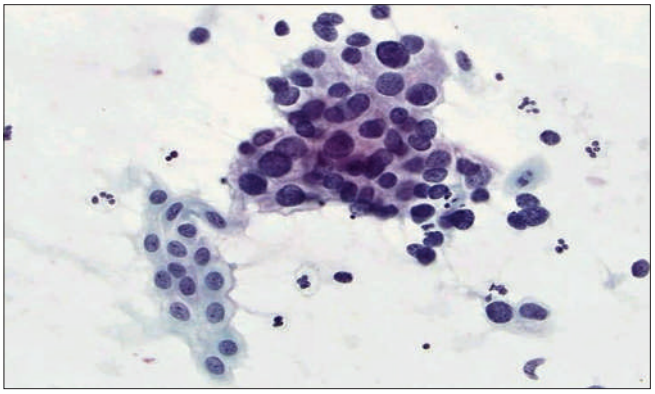

Figure 3: Hsil (400X0– high grade squamous intraepithelial lesion

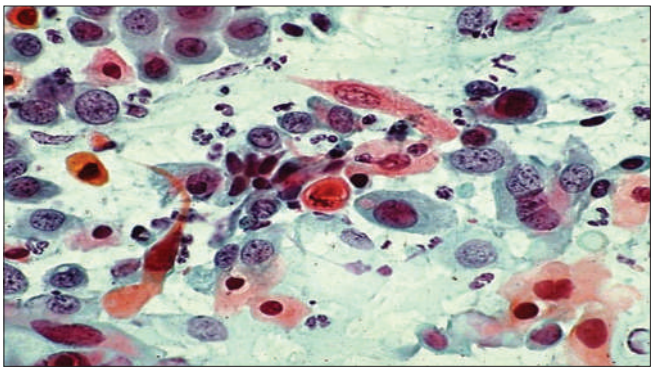

Figure 4: Squamous cell carcinoma (400X)

Low incidence documented by Renuka *et al.*[9] and high incidence by Joshi and Thakur[19] (17% and 12%).Our study correlated with Renuka *et al.* and Joshi and Thakur. In the present study, LSIL and HSIL was 2.5% and 1.5%. Hence, our study correlated with Laxmi *et al.*[7] and Zubair *et al.*[12]

In our study, 8 cases (1%) of SCC was noted. Aruna and Lahari and Bharathi[18] documented 2 cases (0.4%), Zubair *et al.* (0.2%),[12] Bal *et al.* (1%),[20] Bukhari *et al.*[21] (1.4%), and Nandwani *et al.*[22] (3.5%). The present study correlated with Bal *et al.* and differed with Bukhari *et al.* and Nandwani *et al.*

In the present study, 4 cases (0.5%) of AGUS was noted in 40–70 years. Lahari and Bharathi documented 3 cases

of AGUS (0.6%) in 31–60 years. Our study differed with Lahari and Bharathi.[18] Bukhari *et al.*[21] (2012), Nandwani *et al.*[22] (2016), and Zubair *et al.*[12] (2019) documented the AGUS as 0.4%, 0.4%, and 0.9%. The study correlated with Bukhari *et al.* and Nandwani *et al.*

Lahari and Bharathi[18] documented 386 cases(77.2%) Zubair *et al.*[12] 504 cases (90.8%) of NILM. The present study (32.2%) differed with the above author studies.

Verma *et al.*[23] (2022) reported ASCUS 2 cases (1%). In the present study, 33 (4.2%) cases were documented. Our study differed with Verma *et al.*

Verma *et al.*[23] documented 11 cases of LSIL (5.5%) and 5 cases of HSIL (2.5%). In the present study, 20/2.5% and HSIL 12/1.5%. The present study correlated with the study of Verma *et al.* in HSIL cases.

CONCLUSION

Our study highlights the conventional PAP smears (with Bethesda system 2014) evaluation to identify specific infections, non-neoplastic and epithelial abnormalities. PAP smears screening test is recommended as regular test in various age group to prevent morbidity and mortality. PAP smear test maybe used in screening the inflammatory lesions to rule out the bacterial vaginosis (to eliminate the need of further vaginal sampling collection) to prevent pelvic inflammatory diseases.

REFERENCES

1. Vijaya LP, SreeGouri SR. Study and analysis of two hundred cervical PAP smears in our hospital. Int J Contemporary Med Res 2016;3:2787-9.
2. Patel MM, Pandya AN, Modi J. Cervical pap smear study and its utility in cancer screening to specify the strategy for cervical cancer control. Nat J Community Med 2011;2:49-51.
3. Bamanikar SA, Chandanwale SS, Baravkar DS, Dapkekar P. Study of cervical pap smears in a tertiary hospital. Indian Med Gaz 2014;148:250-4.
4. Ranabhat SK, Shrestha R, Tiwari M. Analysis of abnormal epithelial lesions in cervical pap smears in Mid-Western Nepal. J Pathol Nepal 2011;1:30-3.
5. Sarma U, Mahanta J, Talukdar K. Pattern of abnormal cervical cytology in women attending tertiary hospital. Int J Sci Res Pub 2012;29:1-4.
6. Alta BL, Prasad U, Shamili MS, Kumar S. Cytological patterns of cervical pap smears with histopathological correlation. Int J Res Med Sci 2015;3:1911-61.
7. Laxmi RC, Shrestha P, Pradhan B. Analysis of cervical cancer screening at Patan hospital Nepal. J Chitwan Med Coll 2018;8:1-4.
8. Vaghela BK, Vaghela VK, Santawani PM. Analysis of abnormal cervical cytology in papanicolaou smears at tertiary care center a retrospective study. Int J Biomed Adv Res 2014;5:47.
9. Tamrakar R, Ranabhat S, Shrestha M, Poudel S, Shrestha S, Khanal B, *et al*. Clinico-pathological analysis of cervical pap smear in patients attending gynecology OPD of a medical college. Eur J Med Sci 2021;3:12-7.
10. Ramu S, Bindu BJ, Murthy N. Pap smear as early diagnostic tool for cervical cancer-a life saviour. Trop J Pathol Microbiol 2018;4:22-6.
11. Tailor HJ, Patel RD, Patel PR, Bhagat VM. Study of cervical pap smear in a tertiary care hospital of South Gujarat, India. Int J Res Med Sci 2016;4:286-8.
12. Zubair AA, Kulkarni S, Preethi M. Cytomorphological patterns of cervical papanicolaou smear abnormalities based on 2014 Bethesda system in North Karnataka region. Trop J Pathol Microbiol 2019;5:251-9.
13. Adad SJ, De Lima RV, Sawan ZT, Silva ML, De Souza MA, Saldanha JC, *et al*. Frequency of *Trichomonas vaginalis*, *Candida* sp and *Gardnerella vaginalis* in cervical-vaginal smears in four different decades. Sao Paulo Med J 2001;119:200-5.
14. Saha K, Sengupta M, Mistry CJ. Cytological findings of conventional cervical papanicolaou smear in a tertiary care hospital. Glob Res Anal 2013;2:149-51.
15. Verma I, Jain V, Kaur T. Application of Bethesda system for cervical cytology in unhealthy cervix. J Clin Diagn Res 2014;8:OC26-30.
16. Mulay K, Swain M, Patra S, Gowrishankar S. A comparative study of cervical smears in an Urban hospital in India and a population-based screening program in Mauritius. Indian J Pathol Microbiol 2009;52:34-7.
17. Patel CB, Shah PC, Bhagat VM. A Role of cervical pap smear as a screening tool in diagnosis of lesions of cervix-a one-year study. Int J Med Sci Public Health 2016;5:1841-5.
18. Lahari NA, Bharathi M. Application of Bethesda system to study cytological pattern of cervical papaincolaou smear in 500 cases at a tertiary care centre. Indian Pathol Oncol 2020;7:58-62.
19. Joshi C, Kujur P, Thakur N. Correlation of Pap smear and colposcopy in relation to histopathological findings in detection of premalignant lesions of cervix in a tertiary care centre. Int J Sci Stud 2015;3:55-60.
20. Bal MS, Goyal R, Suri AK, Mohi MK. Detection of abnormal cervical cytology in papanicolaou smears. J Cytol 2012;29:45-7.
21. Bukhari MH, Saba K, Qamar S Majeed MM, Niazi S, Naeem S. Clinicopathological importance of papanicolaou smears for the diagnosis of premalignant and malignant lesions of the cervix. J Cytol 2012;29:20-5.
22. Nandwani RR, Totade S, Krishnan MG. Cytomorphological evaluation of squamous cell abnormalities observed on cervical smears in government medical college, Jabalpur, India : A five year study. Int J Res Med Sci 2016;4:794-9.
23. Verma A, Verma S, Vashist S, Attri S, Singhal A. A study on cervical cancer screening in symptomatic women using Pap smear in a tertiary care hospital in rural area of Himachal Pradesh, India Middle East Fertil Soc J 2017;22:39-42.

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Original Article

Pattern of Intestinal Obstruction and its Management: A Tertiary Care Hospital-based Study

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Abstract

Introduction: The intestinal obstruction is one of the common abdominal emergencies and is associated with significant morbidity and mortality, especially when if it progresses to bowel ischemia. The diagnosis and management of the patient with intestinal obstruction are one of more challenging emergency that a surgeon can come across. Early diagnosis of obstruction, skillful operative management, proper technique during surgery, and intensive post-operative treatment carries grateful results.

Methods: This present study scheduled for 50 patients which came in emergency trauma center, 40 are male and 10 are female, including 14 years and above age. The study is related to how patients present in emergency trauma center, examination, basic investigation, management, outcome, and hospital stay.

Results: The maximum number of patients were in age group of 30–50, mostly are male of them. 80–90% of patients presents with abdominal distension, vomiting, and abdominal pain. Majority of them are associated with adhesions and bands, malignancy, and stricture. Sixteen patients were operated with resection and anastomosis, 12 with release of adhesions and band, 15 with hemicolectomy with stoma formation and two with herniorrhaphy, and five patients were kept on conservative management.

Conclusion: A Bowel obstruction can either be a dynamic or adynamic obstruction of the small or large intestines, still intestinal obstruction remains an important surgical emergency. Emergency measures should be taken in all intestinal obstruction patients which help to provide a good outcome and less possible post-operative complications and also less mortality. Early operation is mandatory to avoid the development of peritonitis and systemic sepsis associated with multiorgan failure. According to my case study, surgical intervention is must in majority of the patients with intestinal obstruction.

Key words: Intestinal obstruction, mechanical obstruction, intestinal obstruction clinical findings

INTRODUCTION

Intestinal obstruction is defined as obstruction in forward propulsion of the contents of the intestine either due to dynamic, adynamic, or pseudo-obstruction. It is predisposed by varying underlying anomalies and diseases, which are difficult to define preoperatively. Intestinal obstruction can be diagnosed easily, the underlying cause except post-operative adhesions and external hernias are difficult to be diagnosed preoperatively. A grateful result can be achieved if emergency measures taken like early diagnosis of obstruction, pre-operative preparation, skillful operative management, proper technique during surgery, and intensive post-operative treatment. The diagnosis and management of the patient with intestinal obstruction are one of the more challenging emergencies that a general surgeon can come across. Although the mortality due to acute intestinal obstruction is decreasing with better understanding of pathophysiology, improvement in diagnostic techniques, fluid and electrolyte correction, much potent anti-microbials, and surgical management, but still mortality ranges from 3% for simple obstruction to as much as 30% when there is vascular compromise or perforation of the obstructed bowel. This is further influenced by the clinical setting and related comorbidities.[1] Most of the mortalities occurs in elderly individuals who seek late treatment and who are having associated pre-existing diseases such as diabetes mellitus, COPD, and cardiac diseases. Old age, comorbidity,

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non-viable strangulation, and a treatment delay of more than 24 h were significantly associated with an increased death rate.[2] Avicenna, who lived in the medieval period, has had a great influence on the medical knowledge of the world by writing an encyclopaedia of medicine entitled "Qanun of Medicine." According to Qanun, 16 causes are involved in intestinal etiologies of bowel obstruction such as "reeh," mucoid phlegm, abdominal hot and dry distemperament, decreased bile secretion, job, and so on while modern medicine considers some of them, for instance, volvulus, intestinal herniation, worm, intestinal pseudo-obstruction, and opiate.[3] Ambrosis pare (1510–1590) was first to recognize obstruction as a pathological entity. For severe cases, he used mercury in water, lead bullets smeared with mercury.[4] Jonathan Hutchison performed first successful operation for intussusception in 1871 and hirschprung in 1877 reduced intussusception by salt water and enema.[5] Roentgen in 1893 discovered X-ray and Schwartz in 1911 pointed out the virtue of scout film; Kloiber of Germany (1919) emphasized the importance of x-ray in locating the level of obstruction. How toxic substances get accumulated in bowel was described by Whipple and Williams (1926) described influence of anaerobic infection as a cause of toxemia.[6]

METHODS

Average every year, General Surgery Department of tertiary care center of South Gujarat receives 100–150 patients of Intestinal Obstruction and performs 50–70 surgery on patients of Intestinal Obstruction. Conveniently, 50 cases selected for study in criteria of history, clinical examination and radiological examination, 14 years and above age with clinical and radiological evidence based diagnosed, conservative, and operated intestinal obstruction. According to the patient's treatment protocol; history was taken according to criteria such as personal and social history, chief complaint, past history, any operative history, and family history. In Emergency Trauma Centre, Plain X-ray erect abdomen or lateral decubitus to detect fluid gas levels and ultrasound abdomen was performed in all cases. CT scan abdomen done in selected cases of mass abdomen.[7] After the admission along with above procedure, resuscitation with IV fluids especially ringer lactate and normal saline infusion started till hydration and urine output become normal. Ryle's tube and Foley's Catheter carried out and antibiotic prophylaxis started,[8] close observation of all bedside parameters such as pulse rate, blood pressure, respiratory rate, abdominal girth, bowel sounds, tenderness, and guarding was looked. Such individuals are excluded in this study like diagnosed case of strangulation or clinical peritonitis requiring an urgent operative intervention, previously confirmed or strongly diagnosed peritoneal carcinosis, previous obesity surgery, active diagnosed abdominal malignancy or remission of <10 years duration, and recent abdominal surgery within 30 days.[9,10] After resuscitation, patients with signs of acute intestinal obstruction were managed by appropriate surgical procedure after resuscitation. Cases and findings were recorded and photographs were taken. Surgery adopted and criteria for deciding the procedure were noted. Histopathological examination of the specimen of resection/biopsy was done whenever necessary. The post-operative period was monitored carefully and all parameters were recorded hourly basis depending on the patient's general conditions and toxemia. Routine intermittent oxygen inhalation was instituted in patients having strangulation of the bowel to reduce the damage induced by Ischemia. In this large nationwide cohort of patients with adhesive SBO, we found no benefit regarding preventive antibiotic administration in non-operative treatment; however, antibiotic administration was associated with a longer hospital stay. These results did not support routine administration of antibiotics at admission to prevent bacterial translocation.[11]

RESULTS

In my study, total number of cases are 50 in which 40 (80%) are male and 10 (20%) are female, maximum number of patients were from age group 21–30 that is 11 (22%) and least number of patients were between 71 and 80 that is 1 (2%) of the patients [Table 1].

In my study, 50 patients were included in the study and presentation is shown in Table 2. Maximum number of patients among 50 were presented with pain in abdomen 50 (100%) followed by abdominal distention were seen in 49 (98%) patients, vomiting in 41 (82%) patients, fever in 37 (74%) patients, and only a single patient was presented with abdominal lump which was the least common finding in presentation. Resection and anastomosis were done in 16 cases, which included cases of adhesion,

Table 1: The relation between gender-wise age distribution in case of intestinal obstruction

Age groups	Male (*n*=50)	Female (*n*=50)	Total (*n*=50)	Percentage
14–20	6	3	9	18
21–30	7	4	11	22
31–40	9	-	9	18
41–50	8	2	10	20
51–60	7	-	7	14
61–70	2	1	3	6
71–80	1	-	1	2
	40	10	50	100

Table 2: The clinical features present in the case of intestinal obstruction

S. No.	Clinical features	No. of cases (*n*=50)	Percentage
1	Pain in abdomen	50	100
2	Fever	37	74
3	Vomiting	41	82
4	Groin swelling	0	0
5	Abdominal distension	49	98
6	Abdominal lump	1	1
7	Absence of bowel sound	22	44

Table 3: Types of operations

Types of operations	No. of patients (*n*=50)	Percentage
Resection and anastomosis	16	38
Release of adhesions and band	12	24
Hemicolectomy with stoma formation	15	34
Herniorrhaphy	2	4

Table 4: Etiology of intestinal obstruction

Etiology of intestinal obstruction	Numbers of patients (*n*=50)	Percentage (*n*=50)
Adhesions and band	12	24
Hernia	2	4
Malignancy	10	20
TB stricture	3	6
Appendicitis with obstruction	4	8
Worm infestations	1	2
Ileal stricture	9	18
Meckel's diverticulum	5	10
Small bowel gangrene	4	8

Table 5: Following are the parameters that included in my study for pre-operative management, intra, and post-operative management[9,10]

Parameters evaluated in pre-operative management	Parameters evaluated in Intra and post-operative management
Per abdomen findings, vitals (blood pressure, pulse, oxygen saturation, respiratory rate), hemodynamic stability, radiograph or computed tomography, vascular compromise, level of obstruction, content of nasogastric tube, and any comorbid condition (such as hypertension, diabetes, tuberculosis, and HIV)	Level of obstruction or perforation, any positive findings such as malignant mass or perforation or obstruction, viability of bowel loops, vascular compromise, resection/anastomosis and stoma formation, ventilatory support, serum albumin and protein levels, sutures used in operative procedures, bleeding, fever, wound condition, hospital stay duration, and follow-up of the patient

Table 6: Age-wise incidence of intestinal obstruction in different studies

Age group	Present study (*n*=50) (%)	Singh[15] (*n*=50) (%)	Eggelston[16] (*n*=50) (%)
11–20	18	10	12
21–30	22	16	12
31–40	18	18	13
41–50	20	15	13
51–60	14	10	17
61–70	6	6	13

Table 7: Comparison of etiology of intestinal obstruction in different study

Etiology of intestinal obstruction	Present study (*n*=50) (%)	Ellis and Biaraj *et al.*[19] (%)	Ramachandran[15] (%)
Adhesions and band	24	53	23
Hernia	4	26	13.6
Malignancy	20	-	9.3
TB stricture	6	-	8.6
Appendicitis with obstruction		-	18
Ileal stricture		3	2%

Table 8: Comparision study of clinical features in different study

Clinical features	Present study (*n*=50)	Kapan[20] *et al.* in 2012 (*n*=100)
Pain in abdomen	100	100
Fever	74	64
Vomiting	82	90
Groin swelling	0	-
Abdominal distension	98	86
Abdominal lump	1	-
Absence of bowel sound	44	-

Table 9: Comparision study of operative procedure in different study

Types of operations	Present study (*n*=50) (%)	Tiwari *et al.*[21] (*n*=35) (%)
Resection and anastomosis	38	45.7
Release of adhesions and bands	24	14
Hemicolectomy with stoma formation	34	11.42
Herniorrhaphy	4	-

stricture, ileocecal growth, and volvulus of small intestine. Adhesiolysis was done in 12 cases which included post-operative adhesions, inflammatory adhesions, and constricting bands. Hemicolectomy and stoma formation were done in 15 cases [Table 3]. In my study, patients were suffered from fever and respiratory infection after operative procedure.

Among the 50 patients, 24% of patients presenting with obstruction having adhesions with band and malignancy, 20% of patients with malignancy, 18% with stricture, 10%

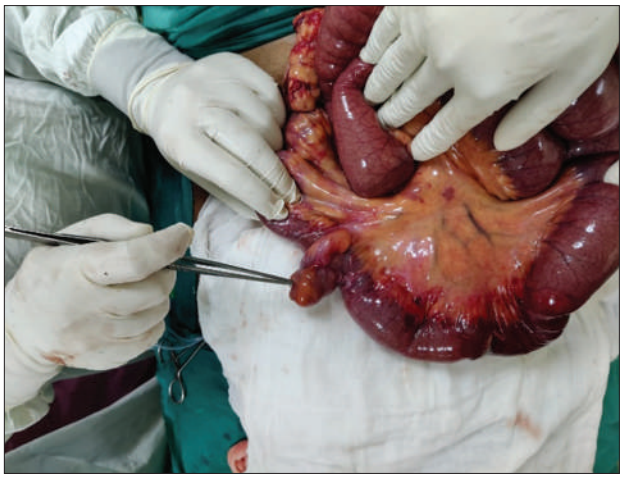

Figure 1: The meckel's diverticulum with vascular compromise of bowel loops

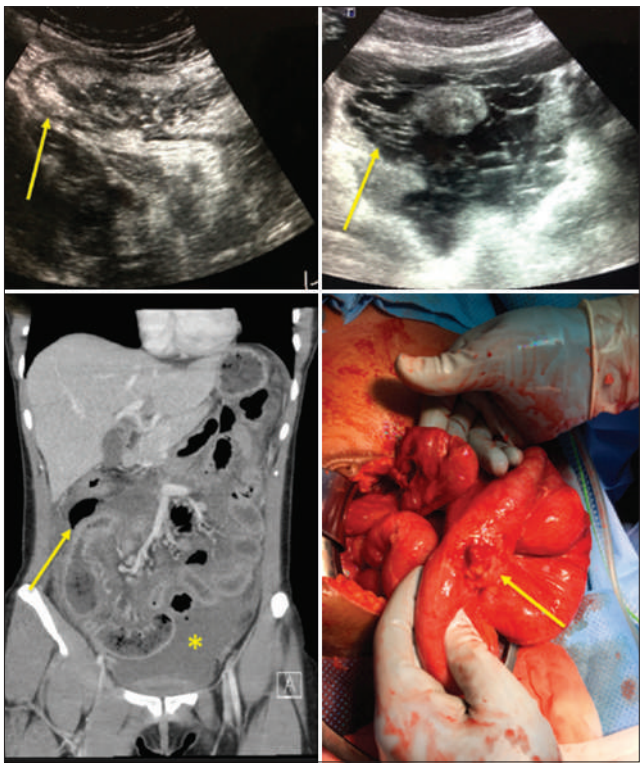

Figure 2: The intestinal tuberculosis[12]

with Meckel's diverticulum, and only one patient present with worm infestations [Table 4].

In my study, 16 patients were operated with resection and anastomosis, 12 with release of adhesions and band, 15 with hemicolectomy with stoma formation and two with herniorrhaphy, and five patients were kept on conservative management.

Non-specific features of the abdominal tuberculosis result in difficulty in establishing a diagnosis. After a diagnosis has been established, prompt initiation of treatment helps prevent morbidity and mortality as it is a treatable disease.[12] Some parameters that included in my study for pre-operative management, intra, and post-operative management [Table 5].

DISCUSSION

Intestinal obstruction is a common surgical problem that surgeons face in usual emergency clinical practice. Each case of intestinal obstruction needs different approach and management. The delay in the treatment will lead to high mortality. since the advancement in understanding the anatomy/physiology, fluid, and electrolyte management along with modern antibiotics and intensive care unit, the mortality has been decreasing consistently. Acute mesenteric ischemia (AMI) is a life-threatening condition that often presents with abdominal pain. Early diagnosis with contrast-enhanced computed tomography and revascularization can reduce the overall mortality in AMI.[13]

I have compared my study with other studies according the criteria such as age incidence, sex incidence, etiology, and malignancy that causing intestinal obstruction. In the study, maximum intestinal obstruction still remains a common and important surgical emergency. Obstruction due to adhesions is increasing in incidence due to increased abdominal and pelvic surgeries. The obstruction due to external hernias is decreasing due to early elective surgeries.[14] Intestinal obstruction occurs in all age groups, but in this case study, maximum cases in seen in age group between 25 and 50 years.

The studies reported by Gillis JR[17] who has reported 17% of cases in the age group of 50–60 years and 60% of the cases of intestinal obstruction occur in the age group of 30–50 years. Singh *et al.*[16] and Ramachandran[15] reported that maximum number of cases occurs in the age group of 25–40 years. In the present cases reported between 25 and 50 years of age group [Table 6]. Intestinal obstruction occurs in specific age groups, according to my study, there are maximum cases seen in male than female, among previous study like Sufian S *et al.*[18] and Shakeed reported maximum cases in male and equal in male and female, respectively.

Studies reported by Ellis and Biaraj *et al.*,[19] found that the maximum cases of adhesions and band seen in intestinal obstruction and Ramachandran[15] found that cases of adhesion and band, malignancy mostly related with intestinal obstruction [Table 7].

In another study done by Halis N *et al*.[20] in 2012, presentation of symptoms and signs analysis shown that, patients with intestinal obstruction most commonly present with pain abdomen and abdominal distension, and most consistent signs are tenderness and increase in bowel sounds [Table 8].

The study reported by Tiwari *et al*.[21] reported operative procedures undertaken according to etiological factors such as adhesiolysis, resection and anastomosis, colostomy, internal hernia reduction, and in my present study, patients were operated like resection and anastomosis (38%), release of adhesions and band (24%), hemicolectomy with stoma formation (34%), and herniorrhaphy (4%) [Table 9]. The pre operative and intra operative findings of my patient; like adhesions in intestinal obstruction in tuberculosis and The meckel's diverticulum with vascular compromise of bowel loops showing in figures[Figures 1 and 2].

CONCLUSION

A bowel obstruction can either be a mechanical or functional obstruction of the small or large intestines, still intestinal obstruction remains an important surgical emergency. All the patients with intestinal obstruction having fluid and electrolyte imbalance so have to be corrected and which should be life-threatening if not corrected, late presentations of the patient with complications possess a challenging problem to the surgeons for management. Early operation is mandatory to avoid the development of peritonitis and systemic sepsis associated with multi organ failure. According to my case study, surgical intervention is must in majority of the patients with intestinal obstruction.

REFERENCES

1. Scott GH, Ramus DL, Michael GS. Maingot's Abdominal Operation. 11th ed. United States: Mc Graw Hill; 2007.
2. Fevang BT, Fevang J, Stangeland L, Søreide O, Svanes K, Viste A. Complications and death after surgical treatment of small bowel obstruction. Ann Surg 2000;23:529-37.
3. Moradi Z, Besharat M, Minaiee B, Aliasl J, Yekta ZP, Toosi MN. Avicenna's view on the etiologies of intestinal obstruction. Iran Red Crescent Med J 2016;18:e20034.
4. Wangensteen OH. Historical aspect of the management of the acute intestinal obstruction. Surgery 1969;65:363-83.
5. Kloiber H. Diagnose des ileus ohne kontrastmittel. Arch F Klin Chir 1919;112:513.
6. Akgun Y, Mann CV. Mesosigmoidoplasty as a definitive operation in treatment of acute sigmoid volvulus. Dis Colon Rectum 1990;39:579-81.
7. Blood Supply to Colon Stock Vector. Illustration of Mouth-186167165. Available from: https://www.dreamstime.com/blood-supply-to-colon-image186167165 [Last accessed on 2022 Sep 17].
8. Ryle's Tube. Brosco-International. Available from: https://www.store.broscointernational.com/gastroenterology-products/ryles_tube [Last accessed on 2022 Jul 10].
9. Courtney M Jr., Townsend B, Evers RM, Beauchamp D, Mattox KL. Sabiston Textbook of Surgery. International Edition. 21st ed. Netherlands: Elsevier; 2020.
10. Bailey HH, Robert J. McNeil Love. Bailey and Love's Short Practice of Surgery. 27th ed., Vol. 2. United States: CRC Press Taylor and Francis Group; 2018.
11. Konishi T, Fujiogi M, Michihata N, Morita K, Matsui H, Fushimi K, *et al*. Comparing outcomes of nonoperative treatment for adhesive small bowel obstruction with and without antibiotics. J Infect Chemother 2021;27:690-5.
12. Debi U, Ravisankar V, Prasad KK, Sinha SK, Sharma AK. Abdominal tuberculosis of the gastrointestinal tract: Revisited. World J Gastroenterol 2014;20:14831-40.
13. Olson MC, Fletcher JG, Nagpal P, Froemming AT, Khandelwal A. Mesenteric ischemia: What the radiologist needs to know. Cardiovasc Diagn Ther 2019;9:S74-87.
14. Naveen N, Mukherjee A, Y NS, Lingegowda S. A clinical study of intestinal obstruction and its surgical management in rural population. J Evol Med Dent Sci 2013;2:3636-50.
15. Selvaraj A, Ramachandran CS. Acute intestinal obstruction due to chylous cyst of meso-ileum. J Indian Med association 1965;44:611-3.
16. Naveen N, Mukherjee A, Nataraj YS, Gowada SNL, *et a*l. Acute intestinal obstruction: A review of 504 cases. JIMA 1973;60:455-60.
17. Herek GM, Gillis JR, Cogan JC. Psychological sequelae of hate-crime victimization among lesbian, gay, and bisexual adults. J Consulting Clin Psychol 1999;67:945-51.
18. Sufian S, Matsumoto T. Intestinal obstruction. Am J Surg 1975;130:9.
19. Ellis H, Moran BJ, Thompson JN, Parker MC, Wilson MS, Menzies D, *et al*. Adhesion related hospital admissions after abdominal and pelvic surgery. Lancet 1999;353:1476-80.
20. Halis N, Sogut O, Guloglu C, Ozgonul A, Gokdemir MT, Durgun HM. Factors associated with morbidity and mortality in patients with mechanical bowel obstruction. Eur J Emerg Med 2012;11:1-5.
21. Tiwari SJ, Mulmule R, Bijwe VN. A clinical study of acute intestinal obstruction in adults-based on etiology, severity indicators and surgical outcome. Int J Res Med Sci 2017;5:3688-96.

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Original Article

Laparoscopic Congenital Inguinal Hernia Repair: A Minimal Invasive Approach

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Abstract

Introduction: Inguinal hernias in children are found in 10–50/1000 live births. Congenital inguinal hernias are due to the persistent processus vaginalis and its repair is necessary because if repair is not done, then it associated with complication such as strangulation and obstruction. So for, better management it deal with laparoscopic repair is done to avoid complication such as injury to vas deferens, post-operative pain, hematoma, wound infection, and recurrence occur with conventional open repair.

Methods: This present study scheduled for 50 patients for laparoscopic repair 43 males and 7 females, between age of 1 and 14 year. Both sexes are included, unilateral and bilateral as well as. One 5-mm and two 3-mm instruments were used to access the peritoneal cavity. Peritoneal incision was made. The internal inguinal ring was closed with a non-absorbable suture. Moreover, intraoperative time, post-operative pain, total hospital stay, wound infection, and testicular atrophy noted.

Results: The maximum number of cases were in the age group year 7–8 (20%) and the minimum number as in the 13–14 age group year (8%). The operating time from skin-to-skin ranged from 25 to 30 min (mean 28.44 min) for unilateral hernia and 35–40 min (mean 39.33 min) for bilateral hernia without conversion and no wound infection with only three cases have post op swelling and less post-operative pain without evident of recurrence.

Conclusion: Laparoscopic herniotomy is feasible and safe in congenital inguinal hernia. There is clear visualization of structures and vas hence less chance to injury. The recurrence rate is less in comparable to that of the traditional open approach with no wound infection, less chance of post-operative swelling, and testicular atrophy with a good cosmetic result.

Key words: Laparoscopy, Congenital hernia, Minimal Invasive approach

INTRODUCTION

Congenital hernia is one of the most common surgical problems in pediatric age group. Patent processus vaginalis is the common etiological factor for congenital hernia. Inguinal hernias in children are found in 10–50/1000 live births.[1] It is higher in premature and low birth weight infants (17–30%). Inguinal hernia is common in boys (M: F = 8:1).[2] Congenital inguinal hernia requires operation, since they have risk for obstruction and incarceration. Under 1 year of age, the incarceration rate is up to 30% which drops to 15% by 18 months age.[3] During recent years, the trend toward laparoscopic approach for hernia repair in children has been increasingly justified. The ability to detect and repair the contralateral opening of internal rings simultaneously, along with safe high ligation of the hernia sac without injury of the vas deference or the spermatic vessels, make laparoscopic approach a reliable alternative to the conventional open technique.[4] Nowadays, laparoscopic hernia repair has obvious advantages, excellent visual exposure including cosmetically better outcomes and identification of the contralateral side.[5] Suturing and closing the internal inguinal ring are the key procedures for laparoscopic hernia repair. The procedure has many variations described in the literature.[6] Intracorporeal techniques refer to the use of laparoscopic instruments to suture the internal ring and tie the knot while avoiding the injury of the vas deferens and vessels.[7] The internal ring is intracorporeally stitched using various methods such as the

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purse-string, Z-type, W-type, or flip-flap suture technique[8] The aim of the study is to focus on the appeal and success of laparoscopic approaches compared to open techniques and to survey which method is likely to survive as the gold standard in the future.

METHODS

The patients attending the department of surgery and also patients referred from other departments of combined tertiary care hospital of south Gujarat, presenting with symptoms and signs of congenital hernia are subjects for our study. Conveniently, selected 50 patients diagnosed to have congenital inguinal hernia between age of 1 and 14 year and scheduled for laparoscopic repair and both sexes are included, unilateral, and bilateral as well as with due consent from the parents. Exclusion criteria included were prematurity, age <1 year, recurrent hernia, and irreducible hernia. Intraoperative findings, post-operative complication such as pain, swelling, wound infection, recurrence, testicular atrophy, and post-operative hospital stay were observed. The patients were placed in a supine position. The operation done under general anesthesia with endotracheal intubation. An infraumbilical incision was made and creating pneumoperitoneum with Co_2 at 10 mmHg using a Veress needle AND then 5 mm telescope was inserted through the 5 mm umbilical port and contralateral site is also observed. Another incision was made in midclavicular line at the level of umbilicus and 3-mm working instruments were introduced. The head of the table was lowered in Trendelenburg's position in some case bowel which was seen to be passing through the ring, which was reduced with non-traumatic bowel grasper. The peritoneum was incised circumferentially at the neck of the sac. The sac was dissected away from spermatic vessels and vas deferens with take care of cord structure and avoids injury to the cord structuresand the landmarks identified included the arching of fascia transversalis, iliopubic tract (IPT), and peritoneal reflection and cord structure. The IPT was approximated to the transversus arch using non-absorbable 2–0 interrupted suture to narrow the internal ring (Lytle's repair) as shown in Figure 1. Too tight approximation was avoided. Patients were routinely discharged on the first sos 2nd post-operative day. All patients were evaluated after 7 days, 1 month, 6 months, and 1 year, and then annually, when possible on out-patient basis.

RESULTS

Total 50 patients were included in this study. The age of the patients ranged from 1 year to 14 year. They were divided into seven groups. The maximum number of cases

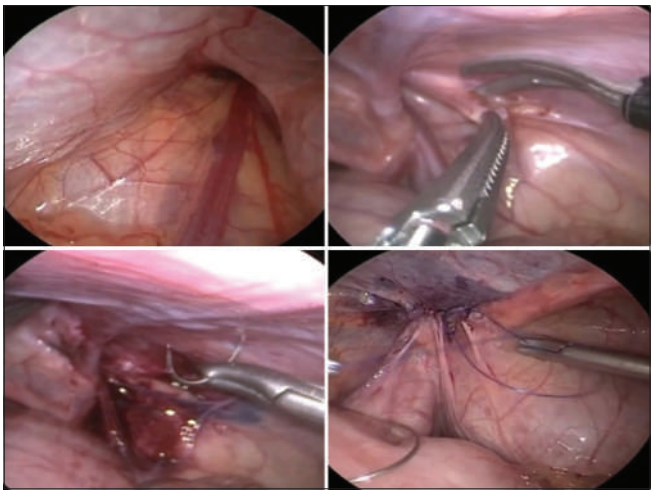

Figure 1: Laparoscopic view of Lytle's repair

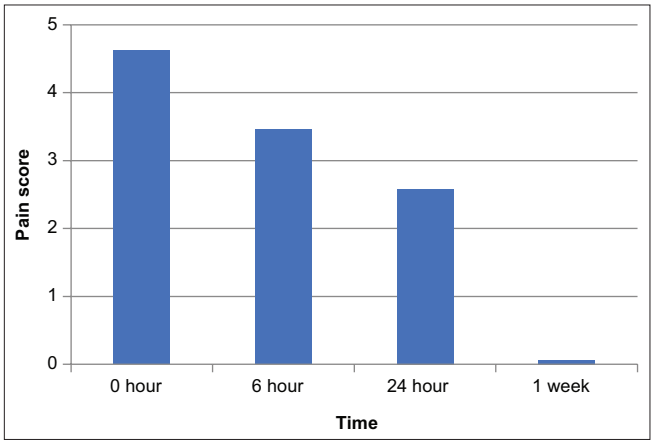

Figure 2: Distribution of post-operative mean pain score with time

were in the age group year 7–8 (20%) and the minimum number was in the 13–14 age group year (8%). The mean age is 6.6 year (SD 3.66) as shown in Table 1. In this study, of 50 children were 43 males (86%) and were seven females (14%), the male-to-female ratio being 6.1:1. Now for the Regarding the site distribution right-sided inguinal hernia found in 30 children, left-sided inguinal hernia in 17 children, and bilateral in 3 children. The operative time ranged from 25 to 38 min (mean 28.44 min) for unilateral and 36–42 min (mean 39.33 min) for bilateral hernia as shown in Table 2. Operative time is calculated from skin incision to skin closure. With experience, this time has gradually decreased. All cases were done laparoscopically without conversion and no intraoperative complications occurred like bleeding, injury of the vas, or vessels or bowel. Scrotal swelling developed in three cases (6%). It resolved by conservative treatment after 2–3 days. All patients were discharged the morning of the next day of operation except in the three cases were stay in hospital for 2 days (6%). On evaluating pain on immediate post-operative, the mean pain

Table 1: Pre-operative evaluation

Total no of cases	50
Sex distribution	Male=43 (86%), Female=7 (14%)
Mean age	6.6 years (SD±3.66)
Side of hernia	Right=30 (60%), Left=17 (34%), bilateral=3 (6%)

Table 2: Intraoperative evaluation

Parameter	Observation
Mean operative duration for	
Unilateral hernia	25–38 min (mean 28.44 min)
Bilateral hernia	36–42 min (mean 39.33 min)
Conversion	No

Table 3: Post-operative evaluation for pain

Pain score	Mean range	SD
0 h	4.62	±0.60
6 h	3.46	±0.50
24 h	2.58	±0.49
1 week	0.06	±0.31

Table 4: Post-operative evaluation

Parameter	Observation
Post-operative swelling	3 cases (6% cases)
Post-operative hospital stay	1 day (94% cases) 2 days (6% cases)
Recurrence	No

score was 4.64 and after 6 h, the mean pain score was 3.46 and it decrease with time after 24 h as shown in Figure 2 and Table 3. On follow-up the pain and scrotal swelling was present only in 1 patient after the 1 week. No wound complications occurred No testicular atrophy was noted.

DISCUSSION

Inguinal hernia repair remains the most common operation performed by pediatric surgeons. It occurs in 0.8–4.4% of all children with higher incidence (up to 30%) in premature babies.[9] All hernias in children are likely to be due to failure of the processus vaginalis to close completely during fetal and new born development. Inguinal hernia will not close spontaneously, and due to the high risk of incarceration, surgical closure is always indicated. Most surgeons recommend repair soon after diagnosis. Conventional herniotomy is considered the gold standard treatment method for PIH.[10] In the past 2 decades, the advances of minimally invasive surgery have completely changed the management of pediatric inguinal hernias.[6,11] In 1975, the first laparoscopic surgery was done in pediatric patient to treat intestinal obstruction and it laid milestone in development of pediatric laparoscopic surgery.[12] In 1997, the first laparoscopic repair of inguinal hernia in pediatric patient was described by El-Gohary.[13] Monteput and Esposito were first to use laparoscopy in the repair of inguinal hernia in male pediatric patient using intracorporeal purse string suture to close the ring.[14]

In 2003, Chan and Tam added intracorporeal hydrodissector to avoid vas and vessel damage.[15] Laparoscopic surgery has been acknowledged for shorter duration of hospital stay and early return to work. Small incision site, less post-operative pain, and early mobilization have made laparoscopic surgery popular among both the patients and the surgeons. In our study, we were able to discharge the patient in 1st post-operative day with full activity and controlled pain. Less post-operative pain is an advantage of laparoscopic surgery. Size of the incision is less than the open herniotomy in congenital inguinal hernia and laparoscopic repair has better cosmesis. Our study was a prospective study that included 50 patients of congenital inguinal hernia. All cases disconnection of the hernia sac was done with closure of peritoneum over internal ring with using non-absorbable 2–0 interrupted suture. The age of the patients varied from 1 year to 14 year. The maximum number of cases were in the age group of 7–8 year (20%) and the minimum number of cases were in the age group of 13–14 year (8%). There were 43 males and were seven females, the male: female ratio being 6.1:1. Among these 50 cases, 30 cases (60%) were on the right side, 17 cases (34%) on the left side, and 3 (6%) cases were bilateral. Mean operative time is 28.44 min in unilateral hernia repair and 39.33 min in bilateral hernia repair.

About 94% of the patient were discharge on the next day, and 6% required 2 days of hospital stay.

CONCLUSION

Laparoscopic inguinal hernia repair in children can be offered, as it is safe, excellent cosmetic results, and reproducible technically easy for experienced laparoscopic surgeons.

REFERENCES

1. Ferguson AH. Oblique inguinal hernia: Typical operation for its radical cure. JAMA 1889;33:6.
2. Boocock GR, Todd PJ. Inguinal hernias are common in pre-term infants. Arch Dis Child 1985;60:669-70.
3. Grosfeld JL. Hernias in children. In: Spitz L, Coran AG, editors. Rob and Smith's Operative Surgery: Pediatric Surgery. London: Chapman and Hall; 1995. p. 222-38.
4. Bharathi RS. Comparative Study of Laparoscopic Versus Conventional Surgery for Congenital Inguinal Hernia in Children [M.S. Thesis], University of Pune; 2008.

5. Abd-Alrazek M, Alsherbiny H, Mahfouz M, Alsamahy O, Shalaby R, Shams A, *et al*. Laparoscopic pediatric inguinal hernia repair: A controlled randomized study. J Pediatr Surg 2017;52:1539-44.
6. Ostlie DJ, Ponsky TA. Technical options of the laparoscopic pediatric inguinal hernia repair. J Laparoendosc Adv Surg Tech A 2014;24:194-8.
7. Lee DY, Baik YH, Kwak BS, Oh MG, Choi WY. A purse-string suture at the level of internal inguinal ring, taking only the peritoneum leaving the distal sac: Is it enough for inguinal hernia in pediatric patients? Hernia 2015;19:607-10.
8. Schier F. Laparoscopic herniorrhaphy in girls. J Pediatr Surg 1998;33:1495-7.
9. Kumar A, Ramakrishnan T. Single port laparoscopic repair of paediatric inguinal hernias: Our experience at a secondary care centre. J. Min Access Surg 2013;9:7-12.
10. Schier F, Danzer E, Bondartschuk M. Incidence of contralateral patent processus vaginalis in children with inguinal hernia. J Pediatr Surg 2001;36:1561-3.
11. Esposito C, Escolino M, Farina A, Settimi A. Two history of decade of laparoscopic pediatric inguinal hernia repair. J Laparoendosc Adv Surg Tech A 2014;24:669-70.
12. Becmeur F. Videosurgery-the second generation. J Pediatr Surg 2011;46:275-9.
13. El Gohary MA. Laparoscopic ligation of inguinal hernia in girls. Pediatr Endosurg Innov Technol 1997;1:185-8.
14. Montupet P, Esposito C. Laparoscopic treatment of congenital inguinal hernia in children. J Pediatr Surg 1999;34:420-3.
15. Chan KL, Tam PKH. A safe laparoscopic technique for the repair of inguinal hernia in boys. J Am Coll Surg 2003;196;987-89.

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Original Article

Mandibular Third Molar Extraction Wound Healing with and Without Combination of Platelet-Rich Fibrin and Beta Tricalcium Phosphate as Grafting Material: A Comparative Prospective Study

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Abstract

Introduction: Bone regeneration of the defects created due to trauma, tumors, or simple procedures such as tooth extractions is still a herculean challenge. Various graft materials and techniques have been proposed over the past century but ideal graft material is still far away from reality.

Aim: The aim of this study is to evaluate the efficacy of beta tricalcium phosphate (β-TCP) in bone regeneration and its synergism when used in conjunction with platelet-rich fibrin (PRF) in enhancement of extraction socket healing.

Materials and Methods: Forty patients were selected and evaluated according to the criteria decided. They were divided into two groups of 20 each depending on the graft to be implanted post extraction. Further the informed consent was taken. Surgical procedure was performed and graft was placed according to their respective study groups under strict aseptic conditions. Radiographic evaluation of the healing socket was done at 3 weeks, 2nd, 4th, and 6th month follow-ups. The scores were compared in the two groups by statistical analysis.

Results: In our study, (Group A) showed consistently better distribution of overall density scores, trabecular pattern scores ($P < 0.001$), significantly higher gray scale values over the period of evaluation compared to corresponding control Group B. Significant increments in bone regeneration at each time interval when compared to baseline (3rd week). By the end of 6 months postoperatively, all the extraction sockets with β-TCP and PRF demonstrated satisfactory bone regeneration within normal limits. Within 6 months satisfactory healing of the extraction sockets was observed in Group A while Group B was lagging quite far behind.

Conclusion: β-TCP shows excellent biocompatibility, bone regeneration potential and also synergistic effects in conjunction with PRF. Thus it can be considered as lucrative, economical, and bone graft substitute in future.

Key words: Beta tricalcium phosphate, Mandibular third molar extraction wound healing, Platelet rich fibrin

INTRODUCTION

Mandibular third molars (M3s) are the most commonly impacted teeth which require surgical extraction and are one of the most frequent surgical procedures in oral surgery.[1] In early 1954 Mead[2] defined an impacted tooth as a tooth that is prevented from erupting into position because of malposition, lack of space, or other impediments. Those teeth that fails to erupt into the dental arch within the expected time are considered impacted.[3] The optimal management of impacted M3s continues to challenge clinicians. An important issue to address is the risk of developing periodontal defects on the distal aspect of mandibular second molars (M2s) after M3 extraction. Kugelberg *et al.*[1-3] published several studies

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documenting the frequency, incidence, and risk factors for M2 periodontal pockets, such as age, inclination of M3, large contact area, visible plaque distal to M2, and pathologically widened follicle of M3, after M3 removal.[4]

Following surgical extraction of the third molar bone loss is observed distal to the second molar which further leads to periodontal pocket formation especially in case of impacted tooth below cervical line (positions B and C); which might lead to sensitivity and periodontal problems; in order to eliminate pocket distal to second molar and to maintain alveolar bone height platelet rich fibrin (PRF) in combination with β tri calcium phosphate is used as a graft material in the extraction socket following surgical extraction of the M3s. Beta tricalcium phosphate (β-TCP) is known to be highly biocompatible, resorbable, and osteo-conductive.

PRF is an autogenous grafting material that shows osteoinductive jelly like consistency, consisting of several growth factors which they are beneficial in accelerating the process of integration of bone substitution. Platelet-rich growth factors are very successful in stimulating bone regeneration and promote healing after the surgical removal of third molar tooth.[5] PRF is both healing and interpositional biomaterial. As a healing material, it accelerates wound closure and mucosal healing due to fibrin bandage and growth factor release. As interpositional material, it avoids the early invagination for undesired cells, thereby behaves as a competitive barrier between desired and undesired cells.[5]

One of the most widely tested calcium phosphate ceramics has been TCP with a nominal composition of Ca_3 (P04)2. This material has a calcium-to-phosphorus ratio of 1:5, TCP is found in two different whitlockite crystallographic configurations, a-TCP, and the more stable β-TCP which is an extremely biocompatible material.[6]

The grafts have the following advantages:

- It is cost effective and minimizing donor site morbidity
- It has only osteo inductive substance so with the combination of β-TCP results in accelerated integration of transplanted bone graft
- Accelerates angiogenesis, multiplication of fibroblasts, and osteoblasts.[7]

With this background the aim of this study was to compare clinically and radiologically the healing of M3s extraction wounds with and without combination of PRF and β-TCP as grafting material.

MATERIALS AND METHODS

The study was proposed to include 40 medically fit patients in the year (2015–2018) of an age group of 18–50 years irrespective of gender having impacted M3s especially (positions b and c) visiting the department of oral and maxillofacial surgery M R Ambedkar Dental College and Hospital, Bengaluru. Patients were included in the study after obtaining ethical clearance from the institution and informed consent from the patients. Forty patients were randomly divided into Groups A and B, 20 patients in each group.

In Group A patients (study group) combination of PRF and β-TCP was placed in extraction socket before closure of the socket.

In Group B patients (control group), the extraction sockets were closed without any intra socket medicaments.

Inclusion Criteria

The following criteria were included in the study:

1. Patients aged between 18 and 50 years who required M3s extractions
2. Patients with the presence of healthy 2nd molar adjacent to impacted mandibular third molar
3. Patients with good general health and good oral hygiene
4. Medically fit patients for surgery under local anesthesia.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients with, periapical infection, or lesions with respect to impacted M3s and 2nd molars
2. Smokers, alcoholics and patients with uncontrolled/ severe systemic diseases
3. Female patients on oral contraceptives, pregnant and lactating mothers
4. Medical conditions or patients taking medication associated with compromised bone healing or medications affecting the number and function of platelets
5. Patients unwilling for follow-up and those patients with incomplete follow-up will be excluded from the study.

Pre-surgical Preparation

The first step was evaluation of patient for the procedure. Pre-surgical evaluation of all patients included intra-oral periapical radiograph/Orthopantomograph/cone beam computed tomography (CBCT).

PRF Preparation

During surgery 10 ml of whole blood was drawn from the patient and transferred into 15 ml sterile glass tube without anticoagulant, which was immediately centrifuged at 3000 rpm for 10 min, after which the blood settles into following three layers: A red thrombus in contact with the red blood corpuscle base, PRF clot in middle, and

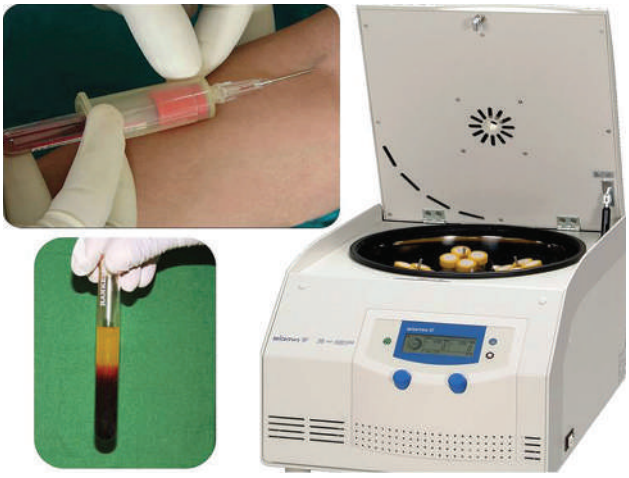
supernatant layer of cellular plasma. The PRF was then stored in a sterile steel bowl till it was placed along with β-TCP into the extraction socket.

Surgical Procedure

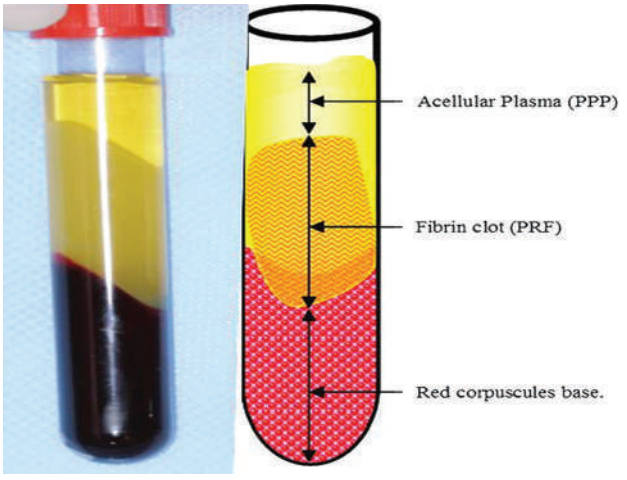
Forty patients were randomly divided into Group A (study group) and Group B (control group), 20 patients in each group. Surgical extraction of impacted third molar was performed under local anesthesia in both groups using routine ward's and modified ward's incision according to the bone exposure required [Figure 1].

In Group A (study group) after extraction 2–3 PRF clots were divided into small pieces and mixed with β-TCP granules was placed in the extraction socket before closure of the socket with non resorbable sutures (3–0 black braided silk) [Figure 2].

Group B (control group) where extraction sockets were closed with non resorbable sutures (3–0 black braided silk) to observe normal socket healing [Figure 3].

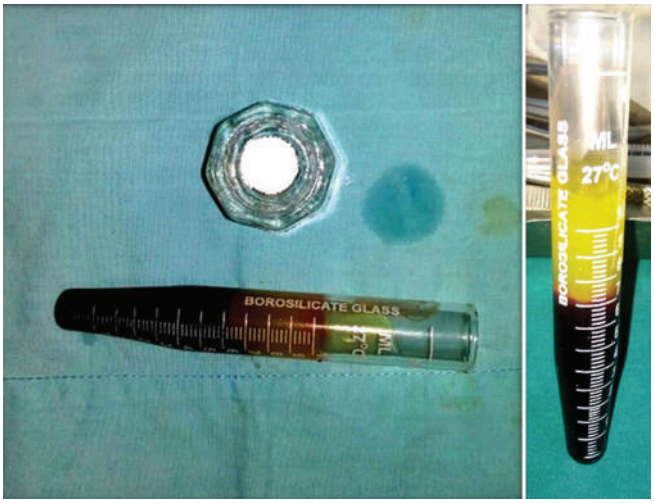


Collection of blood, blood in vacutainer tube after centrifugation, and centrifuge machine.



Blood in the vacutainer tubes after centrifugation at 3000 rpm for 10 min divided into three fractions; lower fraction of red blood cells, middle fraction containing fibrin clot, and upper a cellular plasma fraction.

Isolated platelet-rich fibrin.



Beta Tricalcium Phosphate granules (ß-TCP) (size 0.35–0.5 mm) and Platelet-Rich Fibrin.

For postoperative management, medications were prescribed including clohex mouth wash rinses twice a day for 7 days and, 500 mg amoxicillin 3 times daily for 5 days, analgesics

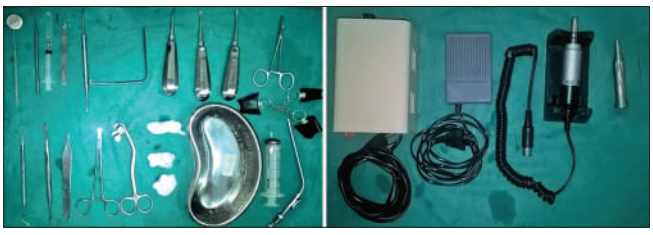


Figure 1: ARMAMENTARIUM

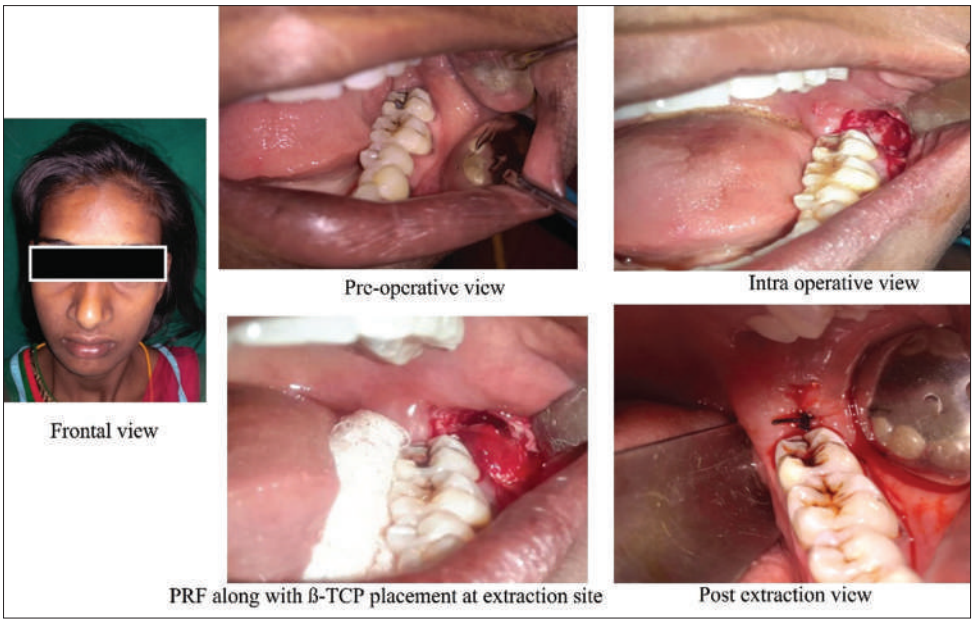


Figure 2: Clinical photographs of extraction socket with graft

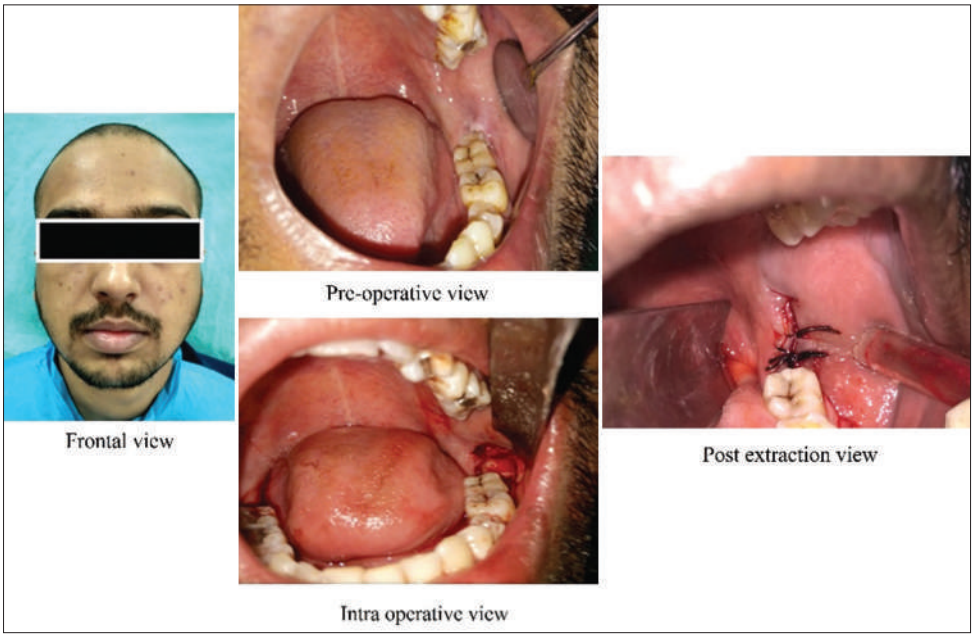


Figure 3: Clinical photographs of extraction socket without graft

for pain in both groups. Post-operative clinical evaluation was done based on bone height, bone density. The patients in both groups were assessed postoperatively on 3rd, 7th, and 14th day for soft-tissue healing. Radiographic assessment for bone healing was done at 3rd week, 2nd month, 4th month, and 6th month CBCT [Figures 4 and 5].

Post-operative assessment of the patient was done under following parameters:

1. Bone height (radiographically and using CBCT)
2. Evaluation of clinical soft tissue and bone healing (using Landry *et al.*, Gonshor healing index and radiographic score).[13]

The data were subjected to Independent Student t-test, ANOVA, and Bonferroni *post hoc* test.

RESULTS

After analysis of the data, the following observations were made:

In case group, there were 20 patients (males 13 and females 7). In control group also, there were 20 patients (males 12 and females 8) [Graph 1]. The patients who had participated in the study were in the age range of 18–50 years with a mean age of 33.83 years.

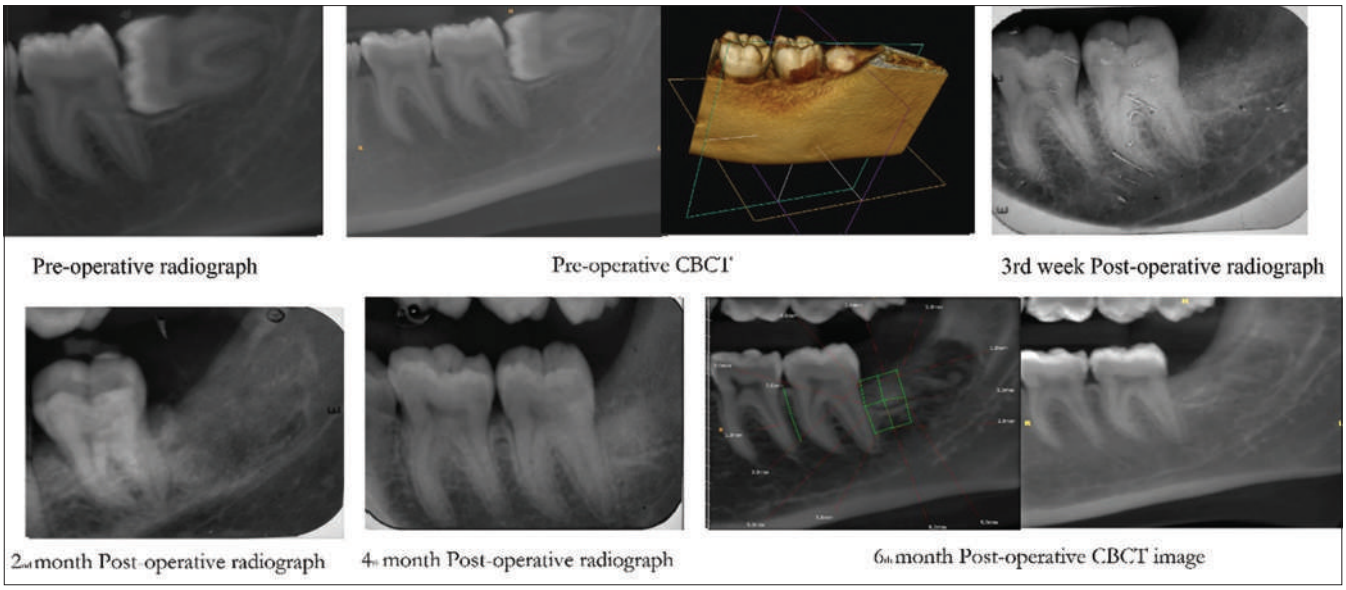


Figure 4: Pre and post extraction radiographs of extraction socket with graft

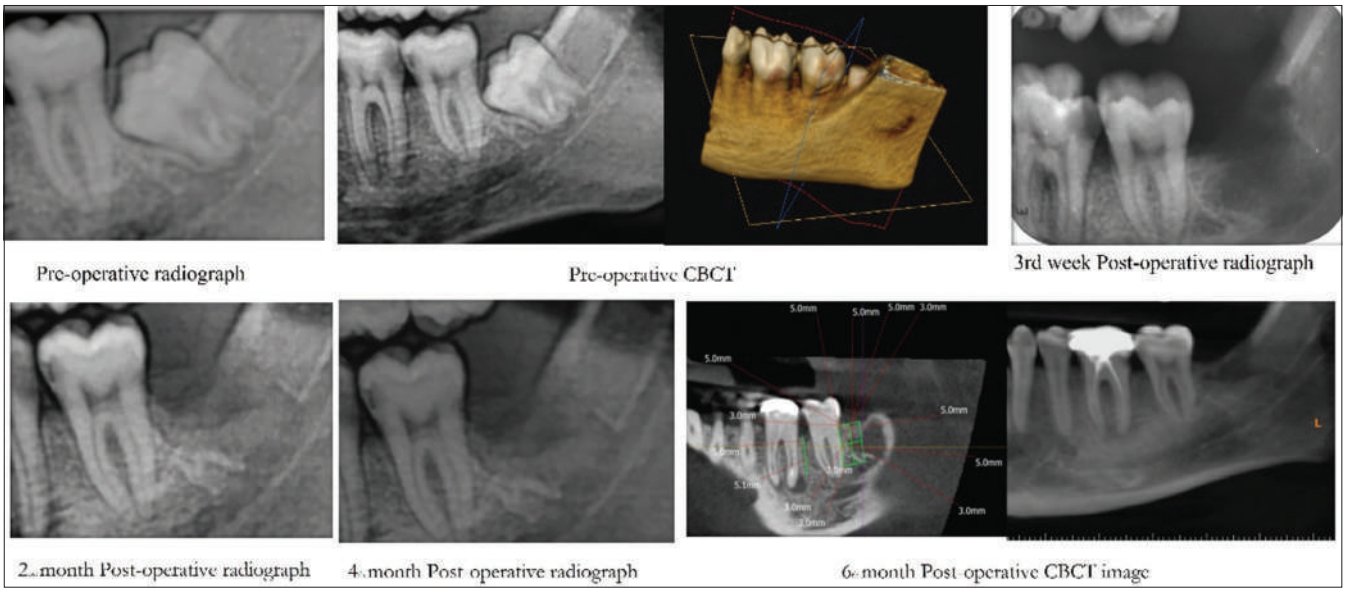


Figure 5: Pre and post extraction radiographs of extraction socket without graft

Table 1: Comparison of soft-tissue healing index scores between study and control groups

Comparison of mean soft-tissue healing index scores between study and control groups at different time intervals using independent student t-test

Time	Group	*n*	Mean	SD	SEM	Mean Diff	t	*P*-value
3D	Study	20	2.65	0.49	0.11	0.50	2.926	0.006*
	Control	20	2.15	0.59	0.13			
7D	Study	20	3.35	0.67	0.15	0.75	4.001	<0.001*
	Control	20	2.60	0.50	0.11			
14D	Study	20	4.20	0.70	0.16	1.10	5.537	<0.001*
	Control	20	3.10	0.55	0.12			

*Statistically significant

Table 2: Comparison of bone healing lamina dura scores between study and control groups

Comparison of mean bone healing lamina dura scores between study and control groups at different time intervals using independent student *t*-test

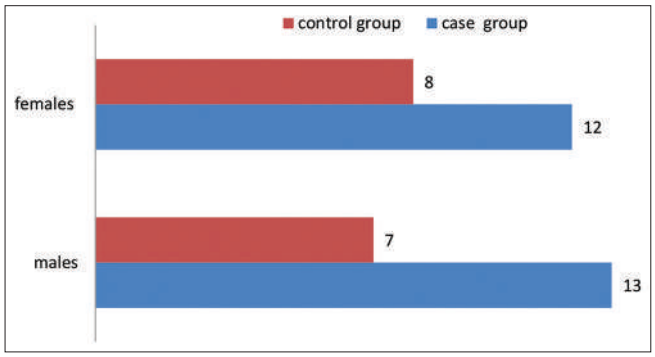
Time	Group	*n*	Mean	SD	SEM	Mean Diff	t	*P*-value
3W	Study	20	−0.10	0.31	0.07	1.40	9.200	<0.001*
	Control	20	−1.50	0.61	0.14			
2M	Study	20	−0.65	0.81	0.18	−0.10	−0.359	0.72
	Control	20	−0.55	0.95	0.21			
4M	Study	20	1.45	1.36	0.30	1.20	2.707	0.01*
	Control	20	0.25	1.45	0.32			

*Statistically significant

Clinical Assessment

Test statistic — Independent student t-test.

Assessment of healing index of soft tissue: Assessment of soft tissue healing by 3rd day for case group showed a mean score of 2.65 and for control group 2.15 ($P = 0.006$). After 7th day for case group mean score was 3.35 and for control group 2.60 ($P = 0.001$). After 14th day for case group mean score was 4.20 and for control group 3.10 ($P = 0.001$) [Table 1].



Graph 1: Gender-wise distribution of the sample

Table 3: Comparison of bone healing overall density scores between study and control groups between study and control groups

Comparison of mean bone healing overall density scores between study and control groups at different time intervals using independent student *t*-test

Time	Group	*n*	Mean	SD	SEM	Mean Diff	*t*	*P*-value
3W	Study	20	1.00	0.00	0.00	2.95	59.000	<0.001*
	Control	20	−1.95	0.22	0.05			
2M	Study	20	−0.60	0.82	0.18	0.60	2.924	0.006*
	Control	20	−1.20	0.41	0.09			
4M	Study	20	0.20	0.41	0.09	0.60	3.126	0.003*
	Control	20	−0.40	0.75	0.17			

*Statistically significant

Table 4: Comparison of mean bone healing trabecular pattern scores between study and control groups

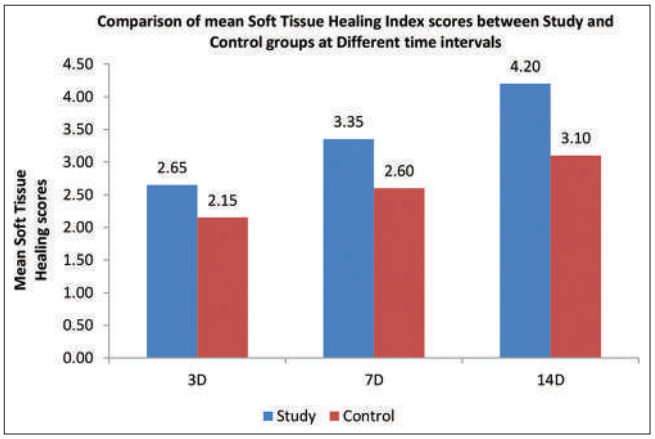
Comparison of mean bone healing trabecular pattern scores between study and control groups at different time intervals using independent student *t*-test

Time	Group	*n*	Mean	SD	SEM	Mean Diff	*t*	*P*-value
3W	Study	20	−1.00	0.00	0.00	0.95	19.000	<0.001*
	Control	20	−1.95	0.22	0.05			
2M	Study	20	0.45	0.51	0.11	1.70	11.235	<0.001*
	Control	20	−1.25	0.44	0.10			
4M	Study	20	1.30	0.47	0.11	2.30	21.877	<0.001*
	Control	20	−1.00	0.00	0.00			

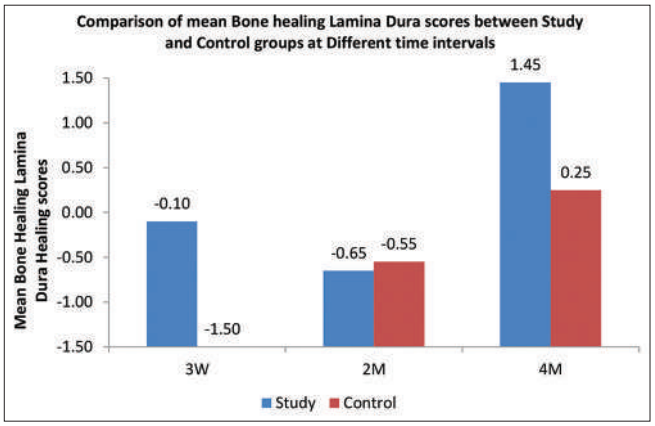
*Statistically significant

Radiographic Assessment

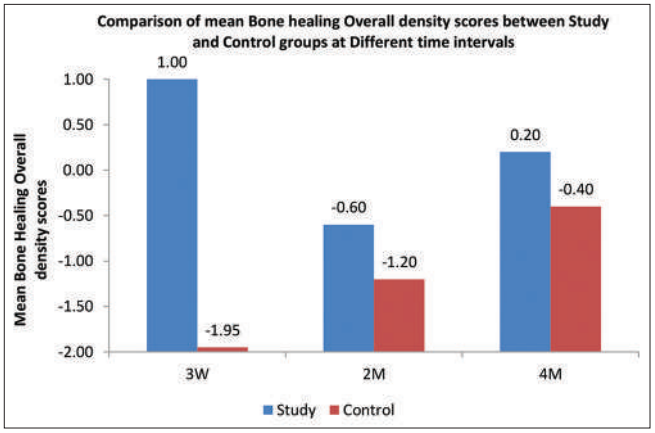
Radiographic assessment at bone healing lamina dura 3rd week for case group showed a mean score of −0.10 and for control group −1.50 ($P = 0.001$). After 2nd month for case group mean score was −0.65 and control group −0.55 ($P = 0.72$). After 4th month for case group mean score was



Graph 2: Comparison of mean soft tissue healing index scores



Graph 3: Comparison of mean bone healing lamina dura scores

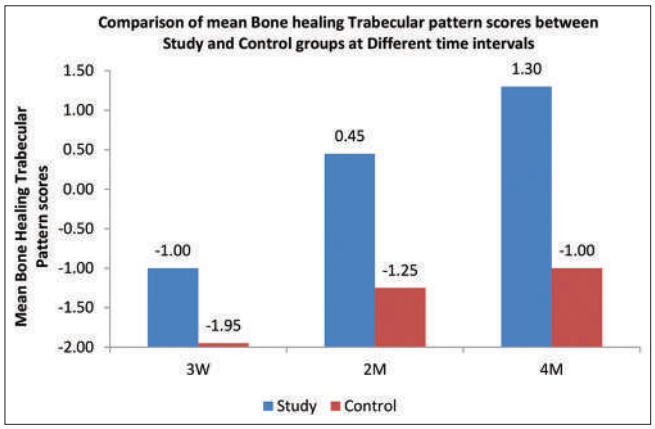


Graph 4: Comparison of mean bone healing overall density scores

1.45 and control group 0.25 ($P = 0.01$) [Table 2 and Graph 3].

Bone healing overall density 3rd week for case group showed a mean score of 1.00 and for control group −1.95 ($P = 0.000$). Bone healing overall density 2nd month for case group the mean score was −0.60 and for control group −1.20 ($P = 0.60$). Bone healing overall density 4th month for case group the mean score was 0.20 and for control group −0.40 $P = 0.60$) [Table 3 and Graph 4].

Bone healing trabecular pattern 3rd week for case group showed a mean score of −1.00 and for control group −1.95 ($P = 0.001$). Bone healing trabecular pattern 2nd month for case group the mean score was 0.45 and for control group −1.25 ($P = 1.70$). Bone healing trabecular pattern 4th month for case group the mean score was 1.30 and for control group −1.00 ($P = 0.001$) [Table 4 and Graph 5].



Graph 5: Comparison of mean bone healing trabecular pattern scores

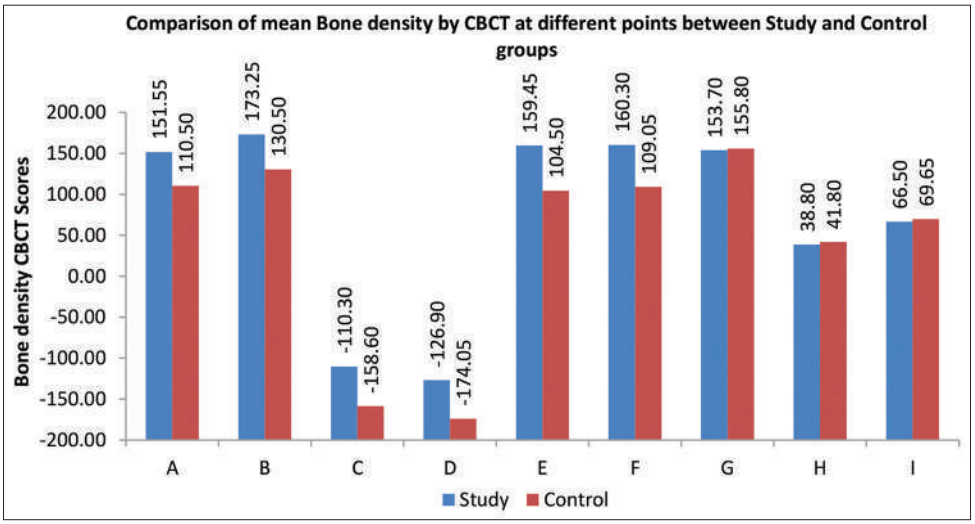
DISCUSSION

The optimal management of impacted M3s continues to challenge clinicians. An important issue to address is the risk of developing periodontal defects on the distal aspect of M2s following M3 extraction.[4,14]

Bone defects represent a medical and socio-economic challenge. Every year, millions of people suffer from bone defects arising from trauma, tumor, or bone diseases or minor dental procedures such as tooth extraction. Successful, satisfactory repair/reconstruction of these bone defects is still a herculean challenge for orthopedic, reconstructive, and maxillofacial surgeons.[15]

In past literature on the uncomplicated healing of experimental extraction wounds, as early as 1923, the work of the following authors is remarkable Euler, W. Meyer, Schram, Steinhardt, Balogh, Kittner, H. Meyer and Deebach. Euler in 1923 established following sequential phenomenon in the healing of extraction wounds: (1) Hemorrhage, (2) coagulation, (3) thrombosis of the vessels of the alveolar wall, (4) beginning of organization of fibrin in the clot, (5) proliferation of the epithelium over the surface of the wound, (6) resorption of the damaged tissue, and (7) formation of new bone.[16]

Almost similar basic sequential cascade of events can be extrapolated to bone defects created due to trauma or tumors. But the difference in the healing of these defects differs owing to the larger size of the defects. Such larger size defects, termed as critical size defect, do not heal completely on its own. These critical size defects require placement of an adjunct graft to assist in the bone formation. These grafts basically either provide an



Graph 6: Comparison of mean bone density by cone beam computed tomography

Table 5: Comparison of mean soft tissue healing index scores between different time intervals in study and control groups

Comparison of mean soft tissue healing index scores between different time intervals in study and control groups using repeated measures of ANOVA FLD by bonferroni *post hoc* test

Group	Time	*n*	Mean	SD	Greenhouse Geisser		*Post hoc* test	
					F	*P*-value	Sig. Diff	*P*-value
Study	3D	20	2.65	0.49	77.610	<0.001*	3D versus 7D	<0.001*
	7D	20	3.35	0.67			3D versus 14D	<0.001*
	14D	20	4.20	0.70			7D versus 14D	<0.001*
Control	3D	20	2.15	0.59	27.243	<0.001*	3D versus 7D	0.03*
	7D	20	2.60	0.50			3D versus 14D	<0.001*
	14D	20	3.10	0.55			7D versus 14D	0.001*

*Statistically significant

Table 6: Comparison of mean bone density by CBCT at different points between study and control groups

Comparison of mean bone density by CBCT in different points between study and control groups at post-Op 6 months using independent student *t*-test

Points	Group	*n*	Mean	SD	SEM	Mean Diff	*t*	*P*-value
A	Study	20	151.55	7.87	1.76	41.05	17.306	<0.001*
	Control	20	110.50	7.11	1.59			
B	Study	20	173.25	7.43	1.66	42.75	17.621	<0.001*
	Control	20	130.50	7.91	1.77			
C	Study	20	−110.30	9.57	2.14	48.30	18.017	<0.001*
	Control	20	−158.60	7.22	1.62			
D	Study	20	−126.90	14.30	3.20	47.15	12.572	<0.001*
	Control	20	−174.05	8.77	1.96			
E	Study	20	159.45	4.43	0.99	54.95	32.239	<0.001*
	Control	20	104.50	6.20	1.39			
F	Study	20	160.30	3.95	0.88	51.25	33.504	<0.001*
	Control	20	109.05	5.59	1.25			
G	Study	20	153.70	4.28	0.96	−2.10	−1.352	0.19
	Control	20	155.80	5.47	1.22			
H	Study	20	38.80	2.76	0.62	−3.00	−3.151	0.003*
	Control	20	41.80	3.24	0.72			
I	Study	20	66.50	3.83	0.86	−3.15	−2.942	0.006*
	Control	20	69.65	2.87	0.64			

*Statistically significant

Table 7: Comparison of bone healing laimna dura scores between different time intervals in study and control groups

Comparison of bone healing laimna dura scores between different time intervals in study and control groups using repeated measures of ANOVA FLD by Bonferroni *post hoc* test

Group	Time	*n*	Mean	SD	Greenhouse Geisser		*Post hoc* test	
					F	*P*-value	Sig. Diff	*P*-value
Study	3W	20	−0.10	0.31	45.288	<0.001*	3W versus 2M	0.01*
	2M	20	−0.65	0.81			3W versus 4M	<0.001*
	4M	20	1.45	1.36			2M versus 4M	<0.001*
Control	3W	20	−1.50	0.61	19.465	<0.001*	3W versus 2M	0.002*
	2M	20	−0.55	0.95			3W versus 4M	<0.001*
	4M	20	0.25	1.45			2M versus 4M	0.01*

*Statistically significant

Table 8: Comparison of bone healing overall density scores between different time intervals in study and control groups

Comparison of bone healing overall density scores between different time intervals in study and control groups using repeated measures of ANOVA fld by Bonferroni *post hoc* test

Group	Time	*n*	Mean	SD	Greenhouse Geisser		*Post hoc* test	
					F	*P*-value	Sig. Diff	*P*-value
Study	3W	20	1.00	0.00	76.000	<0.001*	3W versus 2M	<0.001*
	2M	20	−0.60	0.82			3W versus 4M	<0.001*
	4M	20	0.20	0.41			2M versus 4M	<0.001*
Control	3W	20	−1.95	0.22	57.318	<0.001*	3W versus 2M	<0.001*
	2M	20	−1.20	0.41			3W versus 4M	<0.001*
	4M	20	−0.40	0.75			2M versus 4M	<0.001*

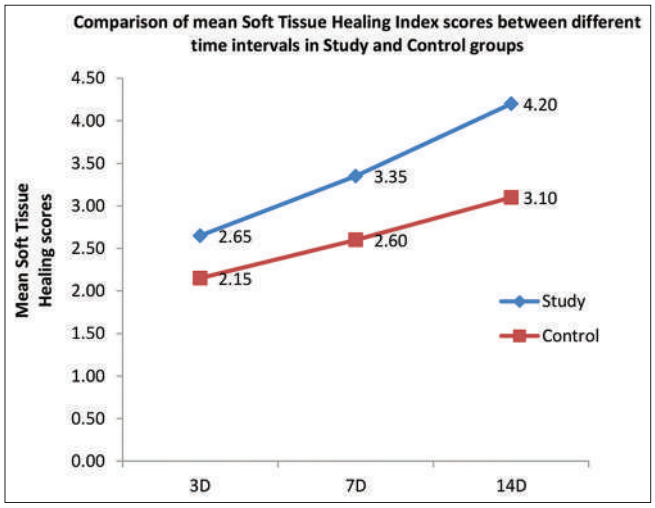
*Statistically significant

Table 9: Comparison of bone healing trabecular pattern scores between different time intervals in study and control groups

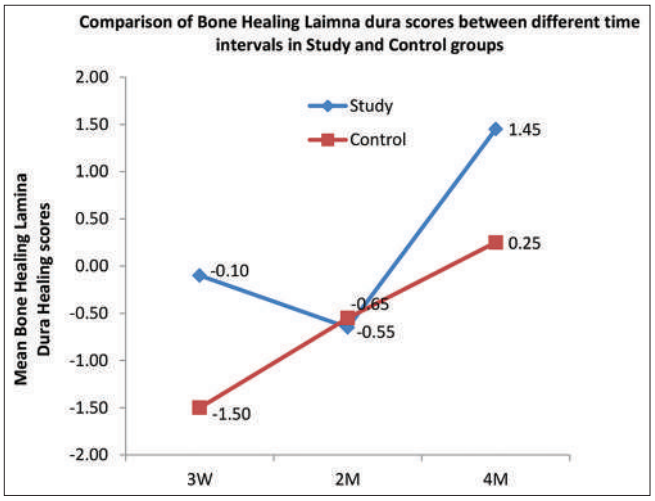
Comparison of bone healing trabecular pattern scores between different time intervals in study and control groups using repeated measures of ANOVA fld by Bonferroni *post hoc* test

Group	Time	*n*	Mean	SD	Greenhouse Geisser		*Post hoc* test	
					F	*P*-Value	Sig. Diff	*P*-Value
Study	3W	20	−1.00	0.00	263.564	<0.001*	3W versus 2M	<0.001*
	2M	20	0.45	0.51			3W versus 4M	<0.001*
	4M	20	1.30	0.47			2M versus 4M	<0.001*
Control	3W	20	−1.95	0.22	62.124	<0.001*	3W versus 2M	<0.001*
	2M	20	−1.25	0.44			3W versus 4M	<0.001*
	4M	20	−1.00	0.00			2M versus 4M	0.06

*Statistically significant



Graph 7: Comparison of mean soft tissue healing index scores

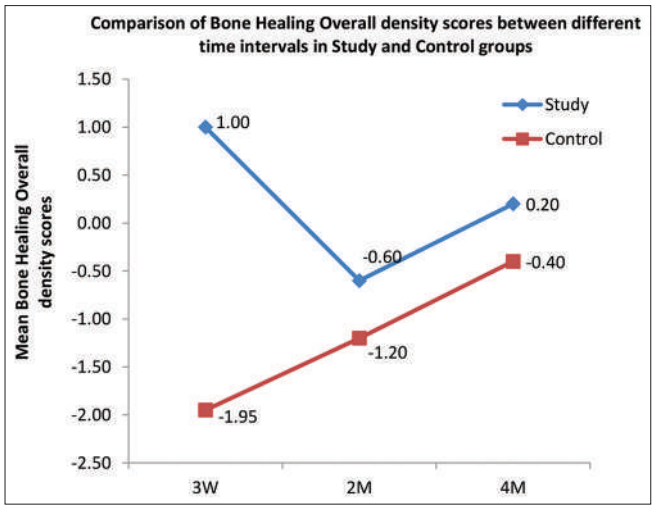


Graph 8: Comparison of bone healing laimna dura scores

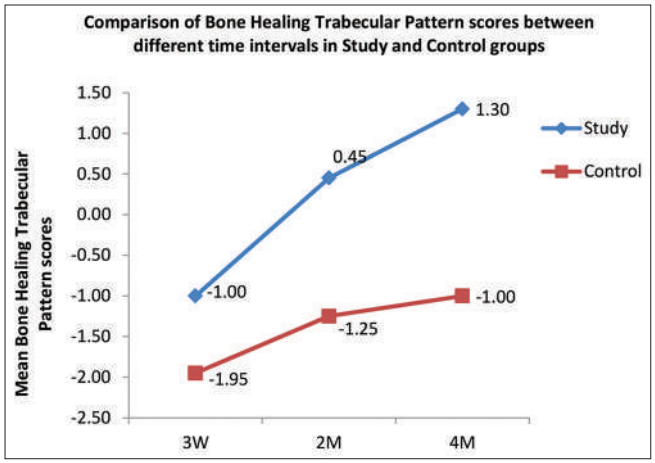
external scaffold for bone regeneration or provide a source of bone regeneration signaling molecules such as bone morphogenic proteins or act as both scaffold and source of essential proteins and other signaling molecules. There is a long history of using autogenic and allogenic bones in the treatment of bone defects.[18,19]

The autograft is the gold standard for repair of bone defects, but there are only a few bones that can be used as donor tissue and frequently result in donor site morbidity. On the other hand, allografts have a high risk of tissue rejection and potential risk of bacterial or viral transmission. Since both these options are highly limited by the age of donors/recipients and their availability, there has been an increasing demand for synthetic bone substitute as an alternative source for bone regeneration.

The ideal material for bone augmentation should be ostoeconductive as well as osteoinductive as far as possible [Table 6]. It should also provide mechanical strength, avoid



Graph 9: Comparison of bone healing overall density scores



Graph 10: Comparison of bone healing trabecular pattern scores

space for vascularization and tissue infiltration and serve as a carrier for relevant therapeutical factors. This would enable it to harvest the self-healing potentials of the patient through (a) recruiting progenitor cells and promoting their proliferation and differentiation; (b) providing main structural base blocks for the regeneration of new bone; and (c) biocompatibility.[20]

The present study was conducted in our institution to evaluate the effects on bone regeneration using combination of β-TCP and PRF. In our study, we evaluated 40 patients undergoing surgical extraction of M3s divided into two groups and evaluated clinically and radiographically as mentioned in the methodology section.

In our study, combination of β-TCP and PRF (Group A) showed consistently better soft tissue healing in comparison with the control group [Table 5, Graph 2 and 7]. These findings were in support with the study conducted by Dutta *et al.*[21-23]

In our study, combination of β-TCP and PRF (group A) showed consistently better Lamina dura scores, overall density scores and trabecular pattern scores over the period of evaluation compared to scores in control Group B [Tables 2-4, 7-9 and Graphs 8-10]. Overall density scores were also observed to be statistically significant at 3rd week also. This discrepancy can be attributed to the inherent radio opacity of the graft material.

Histogram gray scale values in CBCT, which can be used as representation of bone density, were also compared at different points.[22]

At the level of alveolar crest,

- Point A: 3 mm from the distal aspect of 2nd molar
- Point B: 6 mm from distal aspect of 2nd molar.

At 5 mm below the crest

- Point C: 3 mm from distal aspect of distal root of 2nd molar.
- Point D: 6 mm from distal aspect of distal root of 2nd molar.

At 10 mm below the crest

- Point E: 3 mm from distal aspect of distal root of 2nd molar.
- Point F: 6 mm from distal aspect of distal root of 2nd molar.

Normal bone grey scale value

- Point G: At the level of alveolar crest between 1st and 2nd molar.
- Point H: At 5 mm below the crest between 1st and 2nd molar.
- Point I: At 10 mm below the crest between 1st and 2nd molar.

Group A showed significantly higher gray scale values compared to control group B. In the study group (i.e., combination of PRF and β-TCP), results show significant increments in bone regeneration at each time interval when compared to baseline (3rd week).

By the end of 6 months postoperatively, all the extraction sockets with PRF and β-TCP demonstrated satisfactory bone regeneration within normal limits. While extraction sockets without any dressing still demonstrated mild to moderate bony defects compared to adjacent bony architecture [Table 6 and Graph 6].

These findings were in support with the findings of study conducted by Elmohandes,[22] who proved that the use of combination of PRF and β-TCP can reduce long time needed for new bone formation, as well as the morbidity

risk related to harvesting autogenous bone graft.

Claflin (1936) and Steinhardt had extensively studied healing of uncomplicated extraction sockets and had reported that it takes at least 5–6 months for satisfactory healing of the extraction wound.[19] And after that remodeling of the bone would continue for life long based on the functional stimulations. Jahangiri *et al* (1998) has also reported almost similar time line for healing of uncomplicated extraction socket.[24] In contrast to above landmark studies, in our study the time interval for satisfactory bone regeneration in the study group were noted to be in between 2nd month and 4th month.

CONCLUSION

β-TCP shows excellent biocompatibility, and bone regeneration potential. Furthermore, it showed synergistic effects in conjunction with PRF. The use of combination of PRF and β-TCP can reduce long time needed for new bone formation, as well as the morbidity risk related to harvesting autogenous bone graft. Thus, β-TCP when used in combination with PRF can be considered as osteoconductive, lucrative, economical, and bone graft substitute in future.

REFERENCES

1. López-Ramírez M, Vílchez-Pérez MÁ, Gargallo-Albiol J, Arnabat-Domínguez J, Gay-Escoda C. Efficacy of low-level laser therapy in the management of pain, facial swelling, and postoperative trismus after a lower third molar extraction. A preliminary study. Lasers Med Sci 2012;27:559-66.
2. Archer WH. Oral Surgery: A Step-By-Step Atlas of Operative Techniques. 4th ed. Philadelphia, PA: W.B. Saunders Company; 1966. p. 507-10.
3. Peterson LJ. Principles of management of impacted teeth. In: Contemporary Oral and Maxillofacial Surgery. Vol. 2. Missouri, United States: Mosby; 1998. p. 223-57.
4. Richardson DT, Dodson TB. Risk of periodontal defects after third molar surgery: An exercise in evidence-based clinical decision-making. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:133-7.
5. Raja VS, Naidu EM. Platelet-rich fibrin: Evolution of a second-generation platelet concentrate. Indian J Dent Res 2008;19:42-6.
6. Jarcho M. Calcium phosphate ceramics as hard tissue prosthetics. Clin Orthop Relat Res 1981;157:259-78.
7. Bölükbaşı N, Yeniyol S, Tekkesin MS, Altunatmaz K. The use of platelet-rich fibrin in combination with biphasic calcium phosphate in the treatment of bone defects: A histologic and histomorphometric study. Curr Ther Res Clin Exp 2013;75:15-21.
8. Naik B, Karunakar P, Jayadev M, Marshal VR. Role of platelet rich fibrin in wound healing: A critical review. J Conserv Dent 2013;16:284.
9. Nevins M, Giannobile WV, McGuire MK, Kao RT, Mellonig JT, Hinrichs JE, *et al*. Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: Results of a large multicenter randomized controlled trial. J Periodontol 2005;76:2205-15.
10. Soffer E, Ouhayoun JP, Anagnostou F. Fibrin sealants and platelet preparations in bone and periodontal healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2003;95:521-8.
11. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:638-46.
12. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, *et al*. Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part I: Technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:e37-44.
13. Landry RG, Turnbull RS, Howley T. Effectiveness of benzydamyne HCl in the treatment of periodontal post surgical patients. Res Clin Forums 1988 ;10:105–118.
14. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, *et al*. Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part I: Technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:e37-44.
15. Toffler M, Toscano N, Holtzclaw D, Corso MD, Ehrenfest DD, Ehrenfest DM, *et al*. Introducing Choukroun's platelet rich fibrin (PRF) to the reconstructive surgery milieu. J Implant Adv Clin Dent 2009;1:21-30.
16. Weihs D, Gefen A, Vermolen FJ. Review on experiment-based two and three-dimensional models for wound healing. Interface Focus. 2016;6(5):20160038.
17. Simonpieri A, Del Corso M, Sammartino G, Ehrenfest DM. The relevance of Choukroun's platelet-rich fibrin and metronidazole during complex maxillary rehabilitations using bone allograft. Part I: A new grafting protocol. Implant Dent 2009;18:102-11.
18. Doiphode AM, Hegde P, Mahindra U, Kumar SM, Tenglikar PD, Tripathi V. Evaluation of the efficacy of platelet-rich plasma and platelet-rich fibrin in alveolar defects after removal of impacted bilateral mandibular third molars. J Int Soc Prev Community Dent 2016;6(Suppl 1):S47-52.
19. Claflin RS. Healing of disturbed and undisturbed extraction wounds. J Am Dent Assoc 1936;23:945-59.
20. Emadi N, Safi Y, Bagheban AA, Asgary S. Comparison of CT-number and gray scale value of different dental materials and hard tissues in CT and CBCT. Iran Endod J 2014;9:283.
21. Dutta SR, Singh P, Passi D, Patter P. Mandibular third molar extraction wound healing with and without platelet rich plasma: A comparative prospective study. J Maxillofac Oral Surg 2015;14:808-15.
22. Elmohandes W. Evaluation of beta tricalcium phosphate mixed with platelet rich fibrin for rehabilitation of atrophic maxilla with implant installation. Int J Oral Maxillofac Surg 2013;42:1261.
23. Yilmaz D, Dogan N, Ozkan A, Sencimen M, Ora BE, Mutlu I. Effect of platelet rich fibrin and beta tricalcium phosphate on bone healing. A histological study in pigs. Acta Cir Bras 2014;29:59-65.
24. Jahangiri L, Devlin H, Ting K, Nishimura I. Current perspectives in residual ridge remodeling and its clinical implications: A review. J Prosthet Dent 1998;80:224-37.

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Original Article

Electroencephalogram and MRI Changes in the Cases of Febrile Seizure Plus and Complex Febrile Seizure in a Tertiary Care Hospital of West Bengal, India

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Abstract

Introduction: Febrile seizure (FS) is a relatively common childhood condition. This is one of the most frightening and distressing condition for the parents if they have no previous encounter with seizures. However, it is not as harmful and frightening as it appears to be, as FSs do not increase the risk of mortality, mental retardation, or cerebral palsy in these children.

Aims: The aims of this study were to find out any significant magnetic resonance imaging (MRI) changes in complex FSs (CFS), to determine the electroencephalogram (EEG) changes at least after 2 weeks of seizure in "FS plus" and "CFS," and to compare the EEG changes in "FS plus" versus "CFS."

Materials and Methods: The present study was a hospital-based cross-sectional observational study. This study was conducted from November 2021–October 2022 in Burdwan Medical College and Hospital.

Results: EEG was done in all CFS and FS PLUS cases after 2 weeks. EEG changes not found in majority of children. Total we found four EEG changes, one in FS PLUS group, and three in CFS group. This is 5.5% in FS PLUS group and 13.6% in CFS group. One FS PLUS patient shows EEG abnormality, cerebral dysrhythmia. In CFS, three patients show EEG changes. One patient shows cerebral dysrhythmia, second EEG change was generalized slowing, and third EEG change of CFS was spike and wave complex.

Conclusion: CFS has more risk of future epilepsy than simple FS plus. Further, EEG and neuroimaging are indicated for the cases which have high risk of future recurrence and epilepsy. Hence, we had done EEG and MRI in all cases of CFS to find out any significant abnormality which can predict its future outcome. However, we did not find any abnormality in MRI and no specific changes in EEG.

Key words: Electroencephalogram, Febrile seizure, Magnetic resonance imaging, Pediatric

INTRODUCTION

Febrile seizure (FS) is a relatively common childhood condition. This is one of the most frightening and distressing condition for the parents if they have no previous encounter with seizures. However, it is not as harmful and frightening as it appears to be, as FSs do not increase the risk of mortality, mental retardation, or cerebral palsy in these children. The only medical consequence of an initial FS is a greater chance of having recurrent FS s and a slight potential risk of later epilepsy.

The prognosis for FS usually has been found to be good. Such seizures are not associated with any detectable brain damage and epilepsy may eventually develop in only a small minority of children who have had multiple FS.[1]

A FS is defined as"seizures that occur between the ages of 6 months and 60 months with a temperature of 38°C or higher, that are not the result of the any central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior a FSs".[2]

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1. Simple FS –it is a primary generalized, usually tonic-clonic in nature, associated with fever, lasting for <15 min, and not recur within 24 h period
2. **FS plus – FSs that continue past the usual age where they are expected to resolve (6 years) and/or accompanied by afebrile generalized or focal seizures
3. Complex FS (CFS) – Fever with seizures with any of the following features: focal and/or prolonged for more than 15 min and/or recur within 24 h and/or have incomplete recovery within 1 h
4. Febrile status epileptics – it is a FS lasting more than 30 min.

Children with CFSs can be said to have a small but identifiable risk for later epilepsy, based on genetic, developmental, and acquired factors. If these children develop persistent temporal lobe seizures, they are likely to continue to experience seizures in later life.

Aim

The aim of this study was to find out any significant magnetic resonance imaging (MRI) changes in CFS.

Primary Objective

The primary objective of this study was to determine the electroencephalogram (EEG) changes at least after 2 weeks of seizure in "FS plus" and "CFS."

Secondary Objective

The secondary objective of this study was to compare the EEG changes in "FS plus" versus "CFS."

MATERIALS AND METHODS

Study Design

This was a hospital-based cross-sectional observational study in Burdwan Medical College and Hospital.

Study Period

This study was November 2021–October 2022.

Inclusion Criteria

The following criteria were included in the study:

1. Children between 6 months and 7 years of age who was admitted with FSs in the inpatient ward
2. Children who are neurologically normal except for the seizure
3. Children of parents who were give the consent to allow their children to participate in the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. Children aged <6 months and >7 years and admitted with fever and seizure
2. Children presenting with isolated seizures without any fever or those having any signs of CNS infection
3. Those children with history of birth asphyxia/developmental delay/epilepsy.

RESULTS AND DISCUSSION

This study was an attempt to find any specific or significant EEG changes in CFS and FS PLUS and compare it if found. As FS PLUS is a new term, we really want to find out whether this new entity is similar to FS or CFS in respect to incidence, age, and duration of seizure or EEG changes. We also tried to find out any significant MRI changes in CFS.

Sex

Here, in our study out of 148 children with FS, male was 85 and female was 63. Hence, 57.4% was male and 43.6% was female. This male preponderance is corroborative with other studies.

In all cases of FSs, 22 cases were of CFS. In 22 CFS patients, 17 were male and five were female, so 77% male and 23% female patients were in total CFS patient. In 18 of FS PLUS patients, male were 10 (55.5%) and female were 8 (44.5%). Yücel *et al.*[3] showed 66% male in all CFS in their study.

Age

In our study, children of FS between 6 month and 7 year were taken. Mean age was 16.3378 ± 9.2262 months. Offringa *et al.*[4] showed that most FS occurs between 6 months and 3 year of age end mean age was 18 months, which is similar to our study [Table 1].

Family History of FS

In this study, total 51 patients of FS had family history of [Table 2] FS, which was 34.5% of total FS. In 22 of CFS patients, nine patients had positive family history of FS, which is 41% of total CFS. Moreover, among the 18 patients of FS PLUS, five patients had positive family history which is 27.8% of total simple FSs (SFS) PLUS.

History of Previous FS

In our study, out of 148 patients, 32 patients previously had a FS episode. Hence, 21% patients had history of previous FS. In 22 CFS cases, three patients had history of previous FS, which is 13.6% of total CFS patient. In 18 FS PLUS cases, four had history of previous FS, which is 22.2% of total FS PLUS.

Type of FS

In our study, total 148 patients enrolled with FS. Twenty-two children comes under the definition of CFS, which

Table 1: Distribution of common parameters

Parameters	Number	Mean	SD	Minimum	Maximum	Median
Age	148	16.3378	9.2262	6.0000	55.0000	12.0000
Duration of seizure (min)	148	9.2973	7.1147	3.0000	50.0000	8.0000
Number of occurrence in first 24 h of febrile seizure	148	1.1689	0.4268	1.0000	3.0000	1.0000
Time between 2nd episode	22	15.4545	4.7079	6.0000	22.0000	16.0000
Duration of fever at onset of seizure (days)	148	1.1081	0.3116	1.0000	2.0000	1.0000

Table 2: Association between family history of febrile seizure: Type febrile seizure

	Type febrile seizure			
Family history of febrile seizure	CFS	SFS	FS plus	Total
No	13	71	13	97
Row %	13.4	73.2	13.4	100.0
Col %	59.1	65.7	72.2	65.5
Yes	9	37	5	51
Row %	17.6	72.5	9.8	100.0
Col %	40.9	34.3	27.8	34.5
Total	22	108	18	148
Row %	14.9	73.0	12.2	100.0
Col %	100.0	100.0	100.0	100.0

CFS: Complex febrile seizure, SFS: Simple febrile seizures, FS: Febrile seizure

is 14.9%. Eighteen children were come under FS PLUS, which is 12.1%. Remaining 108 children were simple FS. Gourabi *et al.*[5] study shown 39 out of 214 (18%) cases were of CFS, in all FS. In these 39 CFS children, 23 were shown repetitive type of convulsion in a single episode of febrile convulsion, which is now we are considering as FS PLUS. This was 23 out of 148 means 15.5%, so our study is corroborative with other studies.

Type of Convulsion

In our study, out of 148 febrile convulsions, 139 patients had GTCS, and nine patients had focal seizure. In 22 cases of CFS, nine cases had focal seizure and 13 cases had GTCS.

Number of Seizure in single episode of FS

In a single episode of FS within 24 h, 126 cases had only one occurrence of seizure. Nineteen cases had two occurrence of seizure within 24 h. Three cases had three episodes of occurrence of seizure [Table 3].

Duration of Seizure

In CFS, the mean duration of seizure (mean± SD) of [Table 1] patients was 21.2727 ± 11.8691. In FS, the mean duration of seizure (mean ± SD) of patients was 7.0556 ± 2.4942. In FS plus, the mean duration of seizure (mean ± SD) of patients was 8.1111 ± 2.3487. Distribution of mean duration of seizure versus type FS was statistically significant ($P < 0.0001$).

Table 3: Association between cause of fever: Type of febrile seizure

	Type febrile seizure			
Cause of fever	CFS	SFS	FS Plus	Total
Ear infection	0	1	0	1
Row %	0.0	100.0	0.0	100.0
Col %	0.0	0.9	0.0	0.7
Gastroenteritis	4	31	4	39
Row %	10.3	79.5	10.3	100.0
Col %	18.2	28.7	22.2	26.4
Respiratory infection	18	67	14	99
Row %	18.2	67.7	14.1	100.0
Col %	81.8	62.0	77.8	66.9
Urinary tract infection	0	9	0	9
Row %	0.0	100.0	0.0	100.0
Col %	0.0	8.3	0.0	6.1
Total	22	108	18	148
Row %	14.9	73.0	12.2	100.0
Col %	100.0	100.0	100.0	100.0

CFS: Complex febrile seizure, SFS: Simple febrile seizures, FS: Febrile seizure

Table 4: Association between EEG CHANGES: Type febrile seizure

	Type febrile seizure			
EEG changes	CFS	SFS	FS Plus	Total
No	19	0	17	36
Row %	52.8	0.0	47.2	100.0
Col %	86.4	0.0	94.4	24.3
Yes	3	0	1	4
Row %	75.0	0.0	25.0	100.0
Col %	13.6	0.0	5.6	2.7
Total	22	108	18	148
Row %	14.9	73.0	12.2	100.0
Col %	100.0	100.0	100.0	100.0

EEG: Electroencephalogram, CFS: Complex febrile seizure, SFS: Simple febrile seizures, FS: Febrile seizure

Distribution of Cause of Fever

In our study, all cases of FS were investigated to find out the cause of fever. Among the 148 cases, number of children with respiratory infection was 99 (66.9%), gastroenteritis was 39 (26.4%), urinary tract infection was 9 (6.1%), and one case had ear infection.

Febrile Status Epilepticus

In our study, out of total 148 FS, eight patients had seizure duration more than 30 min. Hence, eight patients

included under febrile status epilepticus, which is 5.4% of total FS.

EEG Changes

EEG was done in all CFS and FS PLUS cases after 2 weeks. EEG changes were not found in majority of children. We found total four EEG changes, one in FS PLUS, and three in CFS [Table 4]. This is 5.5% in FS PLUS and 13.6% in CFS. One FS PLUS patient shows EEG abnormality, cerebral dysrhythmia. In CFS, three patients show EEG changes that one patient shows cerebral dysrhythmia, second EEG change was generalized slowing, and third EEG change of CFS was spike and wave complex. With all these EEG changes, no management changes were made. These few EEG changes were not the cause of any alteration in diagnosis. Any of these children whether had epilepsy or recurrence of FS will need a long-term follow-up of all cases.

Grill and Ng[6] showed four EEG abnormalities out of 32 cases which are 12.5%. In this study, they taken only cases of SFS PLUS.

Rasool *et al.*[7] showed in their study that they had 15.6% EEG changes in CFS cases. They had done EEG within 48 h.

MRI Changes

In our study, we had done MRI for all CFS cases to observe any changes in MRI following CFS that can predict the future seizure, but all the MRI we had done of CFS were normal.

Teng *et al.*[8] performed a retrospective review of 79 children meeting the criteria for CFSs from whom data had prospectively been collected, though 71 of them were ultimately analyzed. Forty-six of the 71 (65%) patients underwent neuroimaging (either CT scans in the emergency department or MRI within 1 week), and none had any significant intracranial pathology demanding of emergent intervention.

Shinnar *et al.*[9] showed 11.5% MRI changes in total FSE cases.

This study was done for a long period of 7 years and they had taken a large number of cases. However, our study was done for a period of 1 year and samples were smaller than them.

CONCLUSION

FS is a very common condition, most of the cases are benign, but there are some cases which had slight potential risk of later epilepsy. FS plus can have family history or genetic cause.

CFS has more risk of future epilepsy than simple FS. Further, EEG and neuroimaging are indicated for the cases which have repeated recurrences and EEG changes. Hence, we had done EEG and MRI in all cases of CFS to find out any significant abnormality which can predict its future outcome. However, we did not find any abnormality in MRI and no specific changes in EEG.

A total of 148 patients of FS were included in this study aged between 6 month and 7 years. Mean age in this study was 16 months. Among this, 57.4% was male and 43.6% was female.

In our study, 34.5% patients of FS had family history of FS. Most common cause of fever was respiratory infection. The mean duration of seizure was significantly higher in CFS compared to SFS and FS Plus. About 21% patients had history of previous FS. Eight patients included under febrile status epilepticus which is 5.4% of total FS.

REFERENCES

1. Annegers JF, Hauser WA, Elveback LR, Kurland LT. The risk of epilepsy following febrile convulsions. Neurology 1979;29:297-303.
2. Nelson Textbook of Pediatrics. 21st ed. Philadephia, PA: WB Sanders; 2019. p. 1619-29.
3. Yücel O, Aka S, Yazicioglu L, Ceran O. Role of early EEG and neuroimaging in determination of prognosis in children with complex febrile seizure. Pediatr Int 2004;46:463-7.
4. Offringa M, Hazebroek□Kampschreur AA, Derksen□Lubsen G. Prevalence of febrile seizures in Dutch schoolchildren. Paediatr Perinatal Epidemiol 1991;5:181-8.
5. Gourabi HE, Bidabadi E, Cheraghalipour F, Aarabi Y, Salamat F. Febrile seizure: Demographic features and causative factors. Iran J Child Neurol 2012;6:33-7.
6. Grill MF, Ng YT. Simple febrile seizures plus (SFS+): More than one febrile seizure within 24 hours is usually okay. Epilepsy Behav 2013;27:472-6.
7. Rasool A, Choh SA, Wani NA, Ahmad SM, Iqbal Q. Role of electroencephalogram and neuroimaging in first onset afebrile and complex febrile seizures in children from Kashmir. J Pediatr Neurosci 2012;7:9-15.
8. Teng D, Dayan P, Tyler S, Hauser WA, Chan S, Leary L, *et al*. Risk of intracranial pathologic conditions requiring emergency intervention after a first complex febrile seizure episode among children. Pediatrics 2006;117:304-8.
9. Shinnar S, Bello JA, Chan S, Hesdorffer DC, Lewis DV, MacFall J, *et al*. MRI abnormalities following febrile status epilepticus in children: The FEBSTAT study. Neurology 2012;79:871-7.

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Original Article

Prolonged QTc Interval as an Indicator of Cardiac Autonomic Neuropathy in Diabetes Mellitus Patients

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Abstract

Background: Cardiac autonomic neuropathy (CAN) is linked with increased risk of cardiac arrhythmias and sudden death from silent myocardial ischemia, and hence, it is a significant contributor to morbidity and mortality in diabetes patients. For diagnosis of CAN, there are several non-invasive diagnostic tests but take a long time and are not appropriate for screening broad population. Numerous studies have indicated that prolonged corrected QT interval (QTc) on electrocardiogram (ECG) is a specific, quick, and accurate way to identify CAN.

Objectives: Examining relationship between QTc interval and diabetic CAN is the purpose of current study.

Methods: This is cross-sectional study conducted among 70 diabetic patients aged >18 years, admitted in KIMS, Bangalore, for period of 1 year. The patients underwent cardiovascular autonomic function tests as outlined by Ewing *et al*., 35 were diagnosed with CAN and 35 were without CAN. Twelve lead that ECG was taken in all 70 diabetic patients and QTc was calculated according to Bazett's formula and compared between both groups. Possible influences of age and duration of diabetes in relationship between prolongation of QTc and CAN were also studied.

Results: Mean QTc interval among patients with DM <5 years was 445.65, 6–10 years was 499.48, 11–15 years was 509.80, and >15 years was 530.44. Mean QTC interval among CAN + 525.43 and in CAN- was 444.46. The cutoff value of prolonged QTc interval between patients with and without CAN was >471 ms (statistically significant – $P < 0.001$) with sensitivity of 100% and specificity of 91.43%.

Conclusion: Comparing CAN+ and CAN- patients, lengthening of QTc interval was more noticeable in the former group. Among CAN+ patients, prolongation of QTc interval became longer as DM duration increased. Therefore, in DM patients, a prolonged QTc interval is a substantial risk factor and also a marker of CAN.

Key words: Cardiac autonomic neuropathy, Diabetes mellitus, Electrocardiogram, QTC interval

INTRODUCTION

Chronic hyperglycemia and abnormalities in the metabolism of carbohydrates, fats, and proteins brought on by deficiencies in insulin production, insulin action, or both are hallmarks of diabetes mellitus. By 2040, the number of persons with diabetes mellitus is expected to increase from the present estimate of 415 million to 642 million. Every country is seeing an increase in the number of persons with type 2 diabetes, and 75% of those individuals reside in developing nations.[1] Diabetes mellitus will likely be a major source of morbidity and death in the future due to its rising prevalence throughout the globe. About 50% of people with long-term type 1 and type 2 diabetes mellitus develop diabetic neuropathy. It might show signs of autonomic neuropathy, polyneuropathy, or both. A typical and often ignored complication of diabetes mellitus is Cardiac autonomic neuropathy (CAN). Damage to the autonomic nerve fibers that innervate the heart and blood vessels causes irregularities in heart rate regulation and vascular dynamics, which is what is known as CAN. In individuals

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with type 2 diabetes mellitus, the prevalence of CAN ranges from 20% to 73%. As it is linked to a high risk of cardiac arrhythmias and sudden death due to silent myocardial ischemia,[2] CAN is a significant source of morbidity and mortality in diabetes individuals. For the diagnosis of CAN, several non-invasive diagnostics have been described. These tests are time-consuming and unsuitable for screening a large number of diabetes patients, while being sensitive and repeatable. Numerous studies have indicated that prolonged corrected QT interval (QTc) in the electrocardiogram is a quick and specific way to identify CAN. Examining the relationship between the QTc interval and diabetic CAN is the purpose of the current investigation.[3]

METHODS

Study Design

The patients were chosen for the study's cross-sectional design based on inclusion and exclusion criteria.

Source of Data

Seventy type 2 diabetes mellitus patients who were hospitalized to the Department of Medicine in KIMS Hospital, Bangalore, Karnataka between September 2021 and September 2022 were chosen for the research.

Inclusion Criteria

Patients with type 2 diabetes mellitus between the ages of 20 and 75 were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. People with type 2 diabetes who have heart failure, high blood pressure, cardiac arrhythmias, or other cardiovascular problems [Table 1]
2. COPD sufferers with type 2 diabetes mellitus
3. People with renal failure who have type 2 diabetes mellitus
4. People with liver problems and type 2 diabetes
5. People with type 2 diabetes who have abnormal electrolytes
6. People suffering from cerebral vascular disorders and type 2 diabetes
7. People using medications that are known to affect QT interval and autonomic function testing
8. Patients using vasodilators, beta blockers, and alpha blockers
9. A patient who has clinically obvious neuropathy from a non-diabetic etiology
10. Anemia.

Tests for Measurement of Cardiac Autonomic Function

According to Ewing *et al.*, cardiovascular responses to several non-invasive cardiac autonomic function tests were used to evaluate cardiac dysautonomia. The following are these:-

Based on the results of the above tests, the autonomic dysfunction in type 2 diabetes mellitus patients is categorized as none, early, definite, and severe.

None

All tests normal or 1 test borderline.

Early

One of three heart rate tests abnormal or two borderlines.

Definite

Two heart rate test abnormal.

Severe

Two heart rate tests abnormal with one or both blood pressure tests abnormal or both borderlines.

The QTC interval was determined by Bazett's formula (QTC = QT/√R-R), and a value exceeding 450 ms for adult men and 460 ms for adult women was considered prolonged.

Statistical Methods

Results were expressed as Mean ± Standard Deviation. Students "t" test was used to compare mean's of different groups. $P < 0.05$ was considered significant.

RESULTS

The group with CAN had a mean age of 58.86 ± 10.134 years. The group without CAN had an average age of 56.89 ± 11.3116 years. It was determined that this difference was not statistically significant.

Among CAN + patients, 2.9% had DM for <5 years, 51.4% had DM for 6-10 years, 22.9% had DM for 11-15 years and 22.9% had DM for >15 years. Among CAN - patients, 71.4% had DM for<5 years, 20.0% had DM for 6-10 years, 5.7% had DM for 11-15 years and 2.9% had DM for >15 years with p value being significant [Table 2].

Mean prolonged QTc interval was 445.65 for patients with DM for <5 years, 499.48 for 6-10 years, 509.80 for 11-15 years and 530.44 for patients with DM for >15 years. Hence with increasing duration of diabetes, the mean prolonged QTc interval also increased [Table 3].

With increasing duration of diabetes, the mean prolonged QTc interval also increases [Table 4].

Mean prolonged QTc interval among CAN + was 525.43 and among CAN - was 444.46 which was statistically significant [Table 5].

In this study, the cut-off value for prolonged QTc interval was >471ms with sensitivity of 100% and specificity of 91.43% [Table 8].

Gender Distribution

Total number of females among CAN + were 13 (37.1%) and among CAN – were 8 (22.9%).

Total number of males among CAN + were 22 (62.9%) and among CAN – were 27 (77.1%).

According to Ewing's criteria, we divided the aberrant autonomic function tests into three categories: early, definitive, and severe. Graph 1 represents percentage of CAN in different stages that is early CAN being 51.43%, definite CAN being 31.43% and severe CAN being 17.14% among the CAN positive patients. Graph 1 represents percentage of CAN in different stages that is early CAN being 51.43%, definite CAN being 31.43% and severe CAN being 17.14% among the CAN positive patients.[4-7]

Duration of DM

The results infer that for 1-year increase in the duration of diabetes, the QTC interval will be significantly prolong by 5.23 ms and this finding is statistically significant at $p<0.001$ and the variability in the QTC interval prolongation will be able to explain by duration of diabetes by 36% [Table 7].

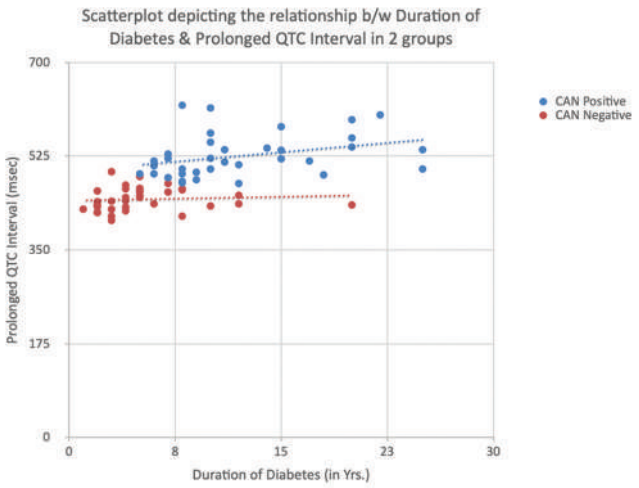


Table 1: Age and gender distribution between two groups

Variable	Category	CAN positive		CAN negative		*P*-value
		Mean	SD	Mean	SD	
Age	Mean	58.86	11.50	56.89	16.43	0.32[a]
	Range	26–81		27–99		
		n	%	*n*	%	
Sex	Male	22	62.9	27	77.1	0.19[b]
	Female	13	37.1	8	22.95	

CAN: Cardiac autonomic neuropathy, a - Mann Whitney test, b - Chi Square test

Table 2: Comparison of duration of diabetes between two groups using Chi-square test

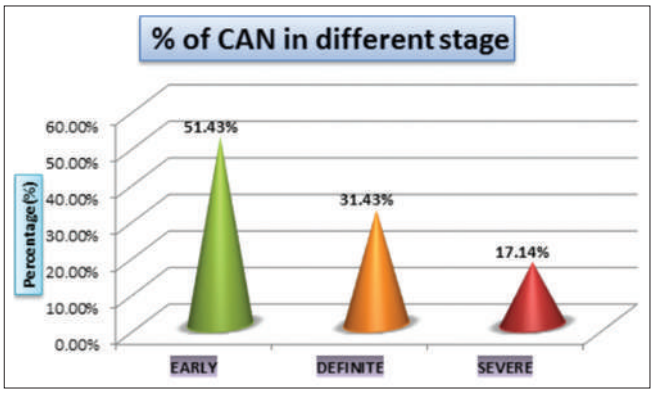
Variable	Category	CAN positive		CAN negative		*P*-value
		n	%	*n*	%	
Duration of diabetes	<5 years	1	2.9	25	71.4	<0.001*
	6–10 years	18	51.4	7	20.0	
	11–15 years	8	22.9	2	5.7	
	>15 years	8	22.9	1	2.9	

CAN: Cardiac autonomic neuropathy, *statistically significant

Table 3: Comparison of mean prolonged QTC interval based on the duration of diabetes using Kruskal–Wallis test

Duration	*n*	Mean	SD	Min	Max	*P*-value
≤5 years	26	445.65	24.10	405	496	<0.001*
6–10 years	25	499.48	50.08	413	620	
11–15 years	10	509.80	44.04	436	580	
>15 years	9	530.44	52.49	434	602	

*statistically significant



Graph 1: %age of CAN in different stages

Table 4: Multiple comparison of mean difference in prolonged QTC interval based on the duration of diabetes using Mann–Whitney *post hoc* test

(I) Duration1	(J) Duration1	Mean Diff. (I – J)	95% CI for the Diff.		*P*-value
			Lower	Upper	
<5 years	6–10 years	−53.826	−84.54	−23.12	<0.001*
	11–15 years	−64.146	−104.94	−23.35	0.001*
	>15 years	−84.791	−127.19	−42.39	<0.001*
6–10 years	11–15 years	−10.32	−51.34	30.7	0.91
	>15 years	−30.964	−73.58	11.65	0.23
11–15 years	>15 years	−20.644	−71.02	29.73	0.70

*statistically significant

Table 5: Comparison of mean Prolonged QTC interval between two groups using Mann–Whitney test

Groups	*n*	Mean	SD	Mean Diff	*P*-value
CAN positive	35	525.43	39.93	80.97	<0.001*
CAN negative	35	444.46	21.35		

*statistically significant

Table 6: Spearman's rank correlation test to assess the relationship between duration of diabetes and prolonged QTC Interval

Variable	Values	CAN positive	CAN negative	Overall samples
Duration of Diabetes	Rho	0.40	0.33	0.68
	P-value	0.02 *	0.06	<0.001 *

CAN: Cardiac autonomic neuropathy, Minus sign denotes negative correlation, The correlation coefficients are denoted by rho, 0.0 – No correlation, 0.01–0.20 – Very Weak Correlation, 0.21–0.40 – Weak Correlation, 0.41–0.60 – Moderate Correlation, 0.61–0.80 – Strong Correlation, 0.81–1.00 – Very Strong Correlation*statistically significant

Table 7: Simple linear regression analysis to predict the prolonged QTC interval using duration of diabetes among study patients

Independent variable	Unstandardized coefficients		t	*P*-value	R^2
	b	Std. Error			
Constant	439.68	8.92	49.275	<0.001*	0.36
Duration	5.23	0.85	6.123	<0.001*	

*statistically significant

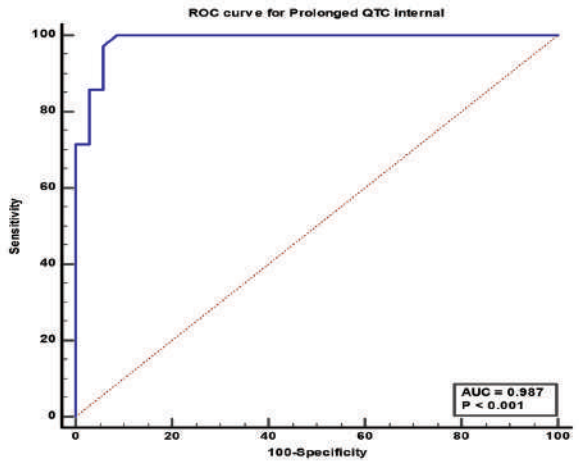


Table 8: ROC curve analysis for prolonged QTC INTERVAL for determining the cutoff between patients with and without cardiac autonomic neuropathy

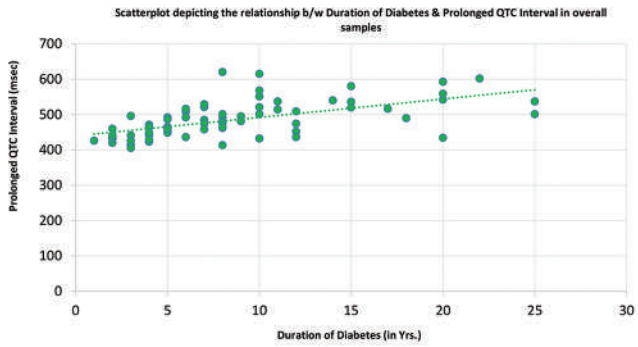
Variable	AUC	Std. Error	95% Conf. Interval		P-value	Cutoff	Sn (%)	Sp (%)
			Lower	Upper				
Prolonged QTC interval	0.987	0.010	0.926	1.000	<0.001*	>471	100.00	91.43

*Statistically significant, ROC is a plot of the true positive rate against the false positive rate for the different possible cutoff points of a diagnostic test. Accuracy is measured by the area under the ROC curve. An area of 1 represents a perfect test; an area of 0.5 represents a worthless test. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system: 0.90–1 = excellent (A), 0.80–0.90 = good (B), 0.70–0.80 = fair (C), 0.60–0.70 = poor (D), and 0.50–0.60 = fail (F)

Table 9: Similar comparable studies

Researcher	CAN	Early	Definite	Severe
Present study	50%	51.43%	31.43%	17.14%
Low *et al*.[12]	73%	NA*	NA	NA
Khandelwal *et al*.[13]	80%	11	0	20
Aggarwal *et al*.[14]	69.23	46	30	24
Manjula *et al*.[15]	74	56	6	0
Hassan *et al*.[16]	72.8	NA	NA	NA
Domuschiev[17]	59.5	NA	NA	NA

CAN: Cardiac autonomic neuropathy, *NA: Not available



DISCUSSION

There was no discernible difference in the mean and SD of QTc between the two groups. The findings of Orosz and Stern investigation, which showed that the QT interval

in DM and pre-DM persons was not longer than normal individuals, are compatible with this observation.[8] Other studies, however, came up with different findings. QTc was substantially longer in DM patients with CAN compared to those without CAN, and this relationship was directly correlated with the severity of CAN. In comparison to our research, the sample size and mean age of their patients were smaller, and their BMI and glycosylated hemoglobin levels were greater.[9] Both sexes met the same standards for long QT distances. The diabetes patients and healthy individuals have been contrasted.[7,10-13] Even in the pre-diabetic stage, long QT intervals might be seen. A change in lifestyle that begins while a person is still in the pre-diabetic stage has a greater impact on the autonomic nervous system's performance. The connection between the QT interval and the CAN is quite intricate. Physicians initially just took into account the relationship between CAN and the prolonged QTc interval.[14] It is unclear if DM or CAN alone are the only causes of extended QT. They both could extend QT and have a synergistic impact.[15-18] With further investigation into the relationship between the QTc prolongation and sympathetic and parasympathetic system activity, the QT distance was established as a measure for the diagnosis of CAN and its severity. This association is controversial, and other research does not support these conclusions.[19] The prolonged QTc interval can be a risk factor for CAN or one of its unfavorable effects. There have been a few isolated reports of people with DM and aberrant heart rate variability with short QTc intervals.[20-22]

In addition, it is hypothesized that the majority of research have been conducted on individuals with DM and CAN and that the long QT interval is more closely related to DM than CAN. Long QT has, however, also been seen in CAN, as well as other illnesses such cirrhosis and sickle cell anemia. This may imply that extended QTc and CAN have separate relationships.[23]

One of the most significant and under recognized complications of diabetes is CAN. After taking into account the numerous inclusion and exclusion criteria, 70 individuals who were determined to have type 2 diabetes mellitus based on ADA criteria in total were included in this research. In this investigation, CAN was ruled out in 50% of the 70 type 2 diabetes. This study's autonomic neuropathy prevalence was quite comparable to the prevalence that has been reported in various previous research.[21]

The mean age of patients with CAN in this research was 58.86 and 56.89 ± 10.134 years, which was comparable to the study done by Hassan *et al.*[16] (50.6 ± 7.8 years), although the mean age in studies done by Motataianu *et al.*[18] and Manjula *et al.*[15] was 59.4 ± 7.9 years and 42 ± 8.9 years, respectively. About 51.43% of the patients in this research had early CAN, 31.43% had definite CAN, and 17.14% had severe CAN. Aggarwal *et al.*[14] discovered early CAN in 46% of patients, four definite in 30%, and severe CAN in 24% of patients. In a similar manner, Ekta *et al.*[13] discovered early CAN in 11% of patients, severe CAN in 20% of patients, and could not classify 69% of patients.[22] Nayak *et al.* discovered that 50% of patients had early CAN and 50% had severe CAN. Early CAN was discovered in 56% of patients and definite CAN in 6%, according to Manjula *et al.*[15] QTc prolongation and cardiac dysautonomia in diabetes mellitus have a well-established relationship. In their research, Bellavere *et al.*[20] suggested that the long QT syndromes should include diabetic CAN. In this research, diabetic individuals with CAN had a longer mean QT interval than those without CAN (525.43 ± 39.93 ms vs. 444.46 ± 21.35 ms). Shimabukuro *et al.* (449 ± 13 ms), Barthwal *et al.* (426 ± 24.4 ms), and Mathur *et al.* (449 ± 21.9 ms) all reported similar findings [Table 9].[19]

Hence, the mean age of CAN positive patients was 58.86 and CAN negative was 56.89. Mean prolonged QTC interval among patients with DM <5 years was 445.65, 6–10 years was 499.48, 11–15 years was 509.80, and >15 years was 530.44.

Mean QTC interval among CAN+ 525.43 and in CAN – was 444.46.

The cutoff value of prolonged QTc interval between patients with and without CAN was >471 ms (statistically significant – $P < 0.001$) with a sensitivity of 100% and specificity of 91.43%.

CONCLUSION

It was discovered that 50% of type 2 diabetics had CAN, and that this incidence was connected with the length of diabetes. A frequent and poorly recognized consequence of diabetes mellitus is CAN. In the development of silent myocardial ischemia, CAN is crucial. Effective prevention of cardiovascular disease-related morbidity and death depends on the early diagnosis of CAN. Cardiovascular autonomic function testing is straightforward yet time-consuming, according to Ewing *et al.* To identify CAN in diabetic individuals, a reasonably simple, rapid, and reliable way is to prolong the QTc interval. Hence,

- The prolongation of QTC interval was more significant among CAN + patients when compared to CAN
- Among CAN+ patients, the prolongation of QTC interval increased with increasing duration of DM
- Hence, prolonged QTC interval is a significant risk factor and also an indicator for CAN among DM patients.

REFERENCES

1. Bennett HP, Knowler WC. Definition, classication of diabetes mellitus and glucose homeostasis. In: Kahn CR, Weir GC, King GL, Moses AC, Smith RJ, Jacobson AM, editors. Joslin's Diabetes Mellitus. Philadelphia: Lippincott Williams and Wilkins; 2003. p. 31.
2. Diabetes: Facts and Gures. International Diabetes Federation. Available from: https://www.idf.org/about-diabetes/facts-gures [Last accessed on 2016 Jul 14].
3. Powers AC, Diabetes mellitus: Complications. In: Kasper DL, Fauci AS, Longo DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. New York: McGraw-Hill Education; 2015. p. 2399.
4. Powers AC, Diabetes mellitus: Complications. In: Kasper DL, Fauci AS, Longo DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. New York: McGraw-Hill Education; 2015. p. 2426.
5. Dimitropoulos G, Tahrani AA, Stevens MJ. Cardiac autonomic neuropathy in patients with diabetes mellitus. World J Diabetes 2014;5:17-39.
6. Vinik AL, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation 2007;115:387-97.
7. Ewing DJ, Clarke BF. Autonomic neuropathy: Its diagnosis and prognosis. Clin Endocrinol Metab 1986;15:855-88.
8. Maser R, Lenhard MJ. Cardiovascular autonomic neuropathy due to diabetes mellitus: Clinical manifestations, consequences, and treatment. J Clin Endocrinol Metab 2005;90:5896-903.
9. Ewing DJ, Martyn CN, Young RJ, Clark BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. Diabetes Care1985;8:491-8.
10. Pappachan JM, Sebastian J, Bino BC, Jayaprakash K, Vijaykumar K, Sujathan P, *et al*. Cardiac autonomic neuropathy in diabetes mellitus: Prevalence, risk factors, and utility of corrected QT interval in the ECG for its diagnosis. Postgrad Med J 2008;84:205-10.
11. Brwone KF, Prystowsky E, Heger JJ, Chilson DA, Zipes DP. Prolongation of the Q-T interval in man during sleep. Am J Cardiol 1983;52:55-9.
12. Low PA, Benrud-Larson LM, Sletten DM, Opfer-Gehrking TL, Weigand SD, O'brien PC, *et al*. Autonomic symptoms and diabetic neuropathy: A population-based study. Diabetes Care 2004;27:2942-7.
13. Khandelwal E, Jaryal AK, Deepak KK. Pattern and prevalence of cardiovascular autonomic neuropathy in diabetics visiting a tertiary care referral center in India. Indian Physiol Pharmacol 2011;55:119-27.
14. Aggarwal S, Tonpay PS, Trikha S, Bansal A. Prevalance of autonomic neuropathy in diabetes mellitus. Curr Neurobiol 2011;2:101-5.
15. Manjula SR, Viswabharti N, Siddhartha K, Neeraja, Sudhakar K. Study of clinical evaluation of autonomic dysfunction in Type 2 DM. IOSR J Pharm Biol Sci 2015;10:55-61.
16. Hassan ZF, Ajeena IM, Abbase AH. The prevalence of cardiac autonomic neuropathy in pure type II diabetic patients. J Nat Sci Res 2014;4:147-55.
17. Domuschiev I. Cardiac autonomic neuropathy and its correlation with retinopathy in Type 2 diabetics. Biotechnol Biotechnol Equip 2005;19:180-3.
18. Moţăţăianu A, Bălaşa R, Voidăzan S, Bajkó Z. Cardiovascular autonomic neuropathy in context of other complications of Type 2 diabetes mellitus. Biomed Res Int 2013;2013:507216.
19. Nayak UB, Acharya V, Jain H, Lenka S. Clinical assessment of the autonomic nervous system in diabetes mellitus and its correlation with glycemic control. Indian J Med Sci 2013;67:13-22.
20. Bellavere F, Ferri M, Guarini L, Bax G, Picolli A, Cardone C, *et al*. Prolonged QT period in diabetic autonomic neuropathy: A possible role in sudden cardiac death? Br Heart J 1988;59:379-83.
21. Mathur CP, Gupta D. QTC prolongation in diabetes mellitus-an indicator of cardiac autonomic neuropathy. J Indian Acad Clin Med 2006;7:130-2.
22. Barthwal SP, Agarwal R, Khanna D, Kumar P. QTC prolongation in diabetes mellitus-an indicator of cardiac autonomic neuropathy. JAPI 1997;45:15-7.
23. Shimabukuro M, Chibana T, Yoshida H, Nagamine F, Komiya I, Takasu N. Increased QT dispersion and cardiac adrenergic dysinnervation in diabetic patients with autonomic neuropathy. Am J Cardiol 1996;78:1057-9.

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Original Article

Prevalence of Psychological Disorder in COVID-19 Patients

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Abstract

Background: COVID-19 has been infecting a sizable amount of individuals worldwide. The pandemic has had negative effects on society's psychological state. Both the pandemic and therefore the measures taken to combat it can affect each individual's psychological state.

Aims and Objectives: Our study aims to assess the prevalence of psychological disorders among admitted COVID-19 patients. Further, we might correlate the association of those symptoms, and therefore, the likely risk factors which may trigger the psychological state problems in this population. This may help in addressing and improving the psychological well-being of the patient alongside the physical aspect. The knowledge regarding psychosocial issues among the infected patients would also guide the implementation of healthcare services and socioeconomic reintegration of society.

Methods: These data were collected on sociodemographic parameters and assessment was done using Hamilton depression rating scale and Hamilton anxiety rating scale at the time of discharge from the hospital.

Conclusion: COVID-19 patients score higher in comorbid anxiety and depression. Moderate-to-severe levels of anxiety and depression are more commonly seen among male patients than female patients.

Key words: COVID-19, Depression, Anxiety, Distress, Insomnia

INTRODUCTION

At present, we are experiencing emotions, thoughts, and situations that we have never experienced before. It is not that there were no pandemics earlier. Pandemics, like "Plague" outbreaks, have been known since times immemorial. The Cholera pandemic and the flu pandemic were highlights of the 19th century. Another "Cholera" Epidemic and the "Spanish-Flu," have ravaged the world in the early part of the 20th century. Subsequently, there have been outbreaks of Asian-Flu, SARS, MERS, EBOLA, etc.,[1,3] The pandemic of COVID-19 is on a completely different scale that it has shaken the whole world and created global panic.[2]

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As COVID-19 initially creeps in and subsequently spreads at a galloping pace, it is been ravaging country after country. The pandemic has significant and variable psychological impacts in each country, counting on the stage of the pandemic. In India, the primary and foremost responses to the pandemic have been fear and a way of clear and imminent danger. Fears have ranged from those supported facts to unfounded fears-supported information and misinformation circulating within the media, particularly social media.[4] At a time when change is the only constant (concerning advisories and precautions, as we move through different stages), what to do? What to not do? questions are near-universal and provide rise to stress and fear. Each folk responds differently to the barrage of data from global and native sources. This will cause those that are "worried well," those that develop distressful psychological symptoms and maladaptive dealing with stress, and people who develop a mental disturbance.[6] The fears of contracting the illness also are frequent and range from misinterpreting every fever or cough as a COVID-19 infection, wanting a test finished reassurance,

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although there are strict guidelines for testing, to hoarding medications despite there not being indications for his or her generalized use. Aside from the advisories regarding hand washing, doubts about whether or to not use a mask, what sort of mask, what distances to take care of, what surfaces need disinfection with what? There also are real worries about job losses and economic slowdown during and following the pandemic.

The list is endless and results in a cycle of concern, worry, and distress. COVID-19 infection intrinsically not only has physical impacts on the well-being of the patients but also has a considerable effect on their psychological state. The various psychological symptoms observed in patients include emotional distress, depression, mood swings, fear of being left alone or being far away from family (isolation), fear of dying, feeling helpless, insomnia, and anxious foreboding. Nervousness and anxiety are most frequently seen in isolation and quarantine wards.[3,4] Studies conducted during this pandemic have recorded a high prevalence of moderate-to-severe depressive and anxiety symptoms among the overall population; particularly among the infected and suspected patients. The common symptoms of COVID-19, such as fever and shortness of breath, can induce anxiety symptoms.[5]

The danger factors that make the patient vulnerable to psychological distress are poor sleep quality, physical symptoms of COVID-19, and therefore the severity of infection. Patients with more symptoms are usually more serious, and therefore, the anxiety symptoms among them increase as they are excessively worried and concerned about the infection and progression of the disease. The sooner research studies have focused on COVID-19-related psychological state issues within the general population, healthcare workers, children, pregnant women, and in people already having a known mental disease. The research data are still limited on the psychological state effects of COVID-19 in infected patients probably because within the infection units, the patient's physical well-being has always been the priority over his psychological assessment; more so in India, where there is a dearth of infrastructure and psychological screening protocols. The patient's mental well-being is usually neglected and compromised during treatment.[5,6]

Hence, our study was planned to assess the prevalence of psychological distress in COVID-19 patients within the sort of anxiety and depression which might further raise the understanding and awareness of the importance of addressing mental health issues in these patients. It will aid in guiding the treatment protocols to focus not only on the physical and medical aspects but also on the psychological state aspect of the infected patients. Early identification of people in the initial stages of psychological distress makes the intervention programs more efficient.[7]

METHODS

This cross-sectional study was done on 100 diagnosed patients of COVID-19 admitted to Sree Balaji Medical College and Hospital COVID Ward. After taking consent, the assessment was done by Hamilton depression rating scale (HDRS) and Hamilton anxiety rating scale (HARS). They were assessed on sociodemographic profile, and therefore, the data were analyzed on different domains of HDRS and HARS.[8,9]

The HDRS (also referred to as Ham-D) is the widely used scale containing 21 items concerning symptoms of depression. The score is calculated from the first 17 items. It has a sensitivity of 86.4% and specificity of 92.2% and has good internal, inter-rater, and retest reliability. The score interpretation is as follows:

Range	Interpretation
0–7	Normal
8–13	Mild depression
14–18	Moderate depression
19–22	Severe depression
>22	Very severe depression

HARS consists of 14 items that measure both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints associated with anxiety). Each item is scored on a scale of 0 (not present) to 4 (severe), with an entire score range of 0–56. It has a sensitivity of 85.7% and specificity of 63.5% and has good reliability and validity. The score interpretation is as follows:[8,9]

- <17-mild
- 18–24-moderate
- 25-severe.

Inclusion Criteria

Diagnosed cases of COVID-19 admitted to Sree Balaji medical college and hospital COVID ward who consent to participation in the study at the time of discharge from the hospital were included in the study.

Exclusion Criteria

The following criteria were excluded form the study:

1. Patient suffering from depression/anxiety disorder/ substance abuse before the diagnosis of COVID-19
2. Patient already receiving any psychotropic drugs
3. Patient with a history of any serious organic illness
4. Patient who does not consent to participation.

RESULTS

Table 1 shows the sociodemographic profile of the 100 COVID-infected patients with 80% males and 20% females. The majority of patients were in the age range of 31–50 years and were educated.

Table 2 shows that 48% of patients had comorbid depression and the majority were in the mild depression category (score range of 8-13 on HDRS) and moderate-to-severe levels of depression were seen more in males than females.

Table 3 shows that 47% of the patients had moderate anxiety (score range 18–24) on HARS. Comorbid mild anxiety was seen more commonly in females (60%) than the male patient (28.75), whereas moderate-to-severe level of anxiety was more in males (71.25%) as compared to females (40%), on the symptom checklist of HDRS [Table 4].

Table 5 demonstrate that the patient had a high score on insomnia (75%), psychic anxiety (40–50), somatic symptoms gastrointestinal (50), muscular (56), respiratory (81), and loss of weight (40).

DISCUSSION

Sociodemographically, in our study, 80% of patients were male and 20% were female [Table 1], these findings are often attributed to the very fact that males are usually the breadwinners of the family in India who leave to supply the family with income and are usually less likely to be stringent in following the security precaution of wearing masks properly and maintaining social distancing. The feminine in our Indian setup, on the opposite hand, is mostly those who occupy homes and look out for youngsters and the elderly. Hence, the risk of getting infected is increased in males.

In our study, out of males, 56.25% were within the age bracket of 31–50 years while among 20% of females, 70% were within the same age group, the rationale behind this age group being the most typical to present with infection is that this age group is that the major productive population within the society who is more concerned about the longer term, economic challenges, and long-term consequences caused by the pandemic. However, the study conducted by Ahmed *et al.* reported that younger age group aged 21–40 reported a higher prevalence of psychological disturbances during the COVID-19 epidemic which was similar to our study.[10]

Table 1: Baseline characteristics of patients

Patients characteristics	Male (*n*=80), *n* (%)	Female (*n*=20), *n* (%)
Age (years)		
<30	15 (18.75)	2 (10)
31–50	45 (56.25)	14 (70)
>50	20 (25)	3 (20)
Educational level		
Up to matric	20 (25)	3 (15)
Matric-graduation	35 (43.75)	10 (50)
>Graduation	25 (31.25)	7 (35)

Table 2: Depression scoring assessment among patients

Scoring	Male (*n*=80), *n* (%)	Female (*n*=20), *n* (%)
No depression	40 (50)	12 (60)
Mild depression	20 (25)	5 (25)
Moderate depression	13 (16.25)	2 (10)
Severe depression	5 (6.25)	1 (5)
Very severe depression	2 (2.5)	0

Table 3: HARS scoring

HARS scoring	Males (*n*=80) *n* (%)	Females (*n*=20) *n* (%)	Total (%)
<17 (mild)	23 (28.75)	12 (60)	35
18–24 (Moderate)	42 (52.5)	5 (25)	47
25 (severe)	15 (18.72)	3 (15)	18

HARS: Hamilton anxiety rating scale

Table 4: HDRS assessment of patients

Symptoms	Male (*n*=80), *n* (%)	Female (*n*=20), *n* (%)
Depressed mood	40 (50)	8 (40)
Insomnia	60 (75)	15 (75)
Work and activity	42 (52.5)	15 (75)
Retardation	15 (18.75)	5 (25)
Agitation	13 (16.25)	5 (25)
Psychic anxiety	35 (43.75)	10 (50)
Somatic symptoms (GI)	40 (50)	10 (50)
Somatic symptoms (general)	18 (22.5)	8 (40)
Hypochondriasis	2 (2.5)	3 (15)
Loss of weight	35 (43.75)	7 (35)
Genital symptoms	2 (2.5)	1 (5)

HDRS: Hamilton depression rating scale

Table 5: HAR assessment of patients

Symptoms	Males (*n*=80), *n* (%)	Females (*n*=20), *n* (%)
Anxious mood	55 (68.75)	15 (75)
Tension	60 (75)	10 (50)
Fear	20 (25)	4 (20)
Insomnia	60 (75)	15 (75)
Depressed mood	40 (50)	8 (40)
Somatic symptoms (muscular)	45 (56.25)	12 (60)
Somatic symptoms (sensory)	15 (18.75)	5 (25)
Respiratory symptoms	65 (81.25)	13 (65)
GI symptoms	40 (50)	10 (50)
Genitourinary symptoms	20 (25)	3 (15)
Autonomic symptoms	25 (31.25)	7 (35)

HAR: Hamilton anxiety rating

As far as psychiatric disorders are concerned, our study shows that 48% of the entire patient had comorbid depression [Table 2]. Out of 80% of males, 50% show depression, and out of 20% of females, 40% have depression. Moderate-to-severe levels of depression were found more in males (25% of 80%) as compared to females (15% of 20%). Self-isolation, travel restrictions, decreased demand for essential commodities, and job interruption, and therefore, the consequent social stigma is the factors that make the patient vulnerable to the event of depressive symptoms. Once they are infected, the economic process involves a halt, workers receive fewer salaries, and a few even lose their jobs. Similar findings were seen in other studies. The study conducted by Huan and Zhao reported a higher prevalence of general anxiety disorder, depressive symptoms, and sleep quality which were 35.1%, 20.1%, and 18.2%, respectively, with a significant difference in the prevalence of anxiety disorder, depression, and sleep quality ($P > 0.05$). Nearly 1/5 of participants with depressive symptoms reported higher psychological pressure, mainly due to hypochondriac concerns (worry about being infected) and a hard-to-control epidemic.[1]

Female patients showed more anxiety symptoms (60% of 20%) as compared to male patients (28.75% of 80%), though the moderate-to-severe level of hysteria was found more in males (71.25% of 80%) as compared to females (40% of 20%) [Table 3], because the females are the key household caretaker of the family, who once infected, are isolated and physically distanced from their children and family. In the Indian context, it is usually seen that a female is more concerned and apprehensive as she has fear of passing the infection to her kids or other vulnerable relations. Many researchers have supported the statement that the severity level of hysteria and depressive symptoms is more in admitted patients.[10,11] Further to this, the study by Zhang *et al.* reported a higher incidence of depression (29.2%) among patients infected with COVID-19; an increasing trend of depression was reported by patients with COVID-19 (21.1%) and the general public (22.4%) compared with the quarantine population. Patients presented with depression and COVID-19 infection were more prone to depressed mood and somatic symptoms when compared with the individuals under quarantine.[12] A higher prevalence of anxiety levels was also reported by the study conducted in the general Iranian population mostly among the females during the COVID-19 outbreak, which was similar to our study.[14]

Similarly, the concerns regarding future sequelae of infection, social stigma, and fear of re-infection may additionally contribute to the event of hysteria and depression in patients. The explanations might be plenty including uncertainty about the treatment, perceived neglect by healthcare workers in fear of getting infected, cost-effectiveness, to be within the isolation wards or quarantine centers, shortage of private protective equipment, intensification of physical symptoms, and uncertainty about the progression of a pandemic. Similar study findings were demonstrated in the Iranian population, where a higher level of anxiety levels among populations with one or more relatives infected families.[14]

On the symptom checklist of HDRS [Table 4] and HAR [Table 5], the majority of the patients showed higher scoring on depressed mood (50% males and 40% females), anxious mood (75% females and 68.75% males), insomnia (75%), and psychic anxiety (males 43.75% vs. females 50%), and physical symptoms (gastrointestinal [50%], general [22.5% in males and 40% in females], muscular [56.25% in males and 60% in females], and respiratory [81.25% in males and 65% in females]). A similar finding was also reported in the Ireland region, where general anxiety (20.0%), depression (22.8%), and general anxiety or depression (27.7%) were the most common psychological distress among patients during the COVID-19 outbreak.[15] Insomnia is one of the most triggering factors in the development of depression and anxiety symptoms among patients. The literature has also supported that poor sleep quality and having more current physical symptoms of COVID-19 have a risk for anxiety and depression among admitted patients.[5,6,12,13,15]

In Indian tradition and culture, family features a role to play altogether sorts of illnesses. However, COVID is peculiar, because it compromises the very social nature of the existence of a private. This social isolation, physical distancing, decreased family connections, and loneliness put the patient in danger of developing anxiety and depressive symptoms. These could also be further aggravated by the infodemic, that is, spreading panic and fear through social media and fragmented information within the print and electronic media.

CONCLUSION

COVID-19 infection has taken a toll on the psychological state of the patients. Anxiety and depression are seen frequently among the infected. These aspects got to be taken into consideration as they affect the general outcome of the patient in physical, psychological, social, and occupational domains of life. The distressing symptoms of hysteria and depression make the individual unproductive and cause social and familial dysfunction within the sort of isolation, loneliness, loss of income, and fear of re-infection or spread of infection to society. The understanding and realization of the association of hysteria and depressive symptoms in COVID-19-infected

patients is important for the early screening and timely psychiatric intervention for a far better functional outcome for the patient. Psychiatric medications and psychological interventions are often planned in terms of short-term also as long-term management. Medication, supportive psychotherapy, and crisis management are required for short-term management behavioral management focusing on individuals. Cognitive behavior modification and group therapy are often planned for the end of the day. The social crisis created by the COVID-19 pandemic might increase inequality, social exclusion, discrimination, and unemployment among patients. Hence, social rehabilitation also becomes as important due to the timely diagnosis and adequate medical aid.

AUTHORS' CONTRIBUTIONS

Dr. P. Kanmani and Dr. A. Sankar are the co-first authors. They are responsible for the integrity of the data and had full access to all data in the study. *Study concept and Designing:* Dr. Umashankar; *Acquisition, analysis and interpretation of data*: Dr. P. Kanmani; *Critical revision of manuscript*: Dr. Umashankar; and *Supervision*: Dr. A. Sankar.

REFERENCES

1. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: A web-based cross-sectional survey. Psychiatry Res 2020;288:112954.
2. Hall RC, Hall RC, Chapman MJ. The 1995 Kikwit Ebola outbreak: Lessons hospitals and physicians can apply to future viral epidemics. Gen Hosp Psychiatry 2008;30:446-52.
3. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, *et al*. The psychological impact of quarantine and how to reduce it: Rapid review of the evidence. Lancet 2020;395:912-20.
4. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, *et al*. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health 2020;17:1729.
5. Wang Y, Xu B, Zhao G, Cao R, He X, Fu S. Is quarantine related to immediate negative psychological consequences during the 2009 H1N1 epidemic? Gen Hosp Psychiatry 2011;33:75-7.
6. Fitzgerald PJ. Serious infection may systemically increase noradrenergic signaling and produce psychological effects. Med Hypotheses 2020;139:109692.
7. Da Silva AM, Vilhena E, Lopes A, Santos E, Gonçalves MA, Pinto C, *et al*. Depression and anxiety in a Portuguese MS population: Associations with physical disability and severity of disease. J Neurol Sci 2011;306:66-70.
8. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
9. Maier W, Buller R, Philipp M, Heuser I. The hamilton anxiety scale: Reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affect Disord 1988;14:61-8.
10. Ahmed MZ, Ahmed O, Aibao Z, Hanbin S, Siyu L, Ahmad A. Epidemic of COVID-19 in China and associated Psychological Problems. Asian J Psychiatr 2020;51:102092.
11. Xiang YT, Yang Y, Li W, Zhang L, Zhang Q, Cheung T, *et al*. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. Lancet Psychiatry 2020;7:228-9.
12. Zhang J, Lu H, Zeng H, Zhang S, Du Q, Jiang T, *et al*. The differential psychological distress of populations affected by the COVID-19 pandemic. Brain Behav Immun 2020;87:49-50.
13. United Nations. The Social Impact of COVID-19 Available from: https://www.un.org/development/desa/dspd/2020/04/social-impact-of-covid-19 [Last accessed on 2020 Dec 02].
14. Moghanibashi-Mansourieh A. Assessing the anxiety level of Iranian general population during COVID-19 outbreak. Asian J Psychiatr 2020;51:102076.
15. Hyland P, Shevlin M, McBride O, Murphy J, Karatzias T, Bentall RP, *et al*. Anxiety and depression in the Republic of Ireland during the COVID-19 pandemic. Acta Psychiatr Scand 2020;142:249-56.

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Original Article

COVID-19-Associated Variations in Liver Function Parameters: A Retrospective Study

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Abstract

Introduction: The coronavirus disease (COVID-19) was declared as pandemic disease by the World Health Organization. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mainly affects the respiratory system. The common symptoms of COVID-19 are fever, cough, fatigue, shortness of breath, expectoration, rhinorrheas, sore throat, diarrhea, loss of smell and taste, etc. In SARS-CoV-2 infection, multi-organ involvement of heart, kidney, pancreas, and liver are also reported. The fundamental aim of the study was to describe clinical characteristics of COVID-19 patients admitted with moderate to severe pneumonia and to find out their relation to the liver parameters.

Methods: This was a descriptive cross-sectional study in 253 COVID-19 patients (157 males and 96 females) with the age range of 20–60 years, which was conducted at Government Medical College, Baramulla from September 2021 to January 2022. Data collection includes recording of demographic parameters (age, gender, and sex). Blood samples of the patients were taken to measure serum liver function parameters.

Results: The result shows elevated levels of alanine transaminase in 24.11% patients, aspartate transaminase in 16.20% patients, total bilirubin in 12.65% patients, total protein in 16.21% patients, albumin in 3.95% patients, and alkaline phosphatase in 16.60% patients. However, reduced globulin levels were found in 3.95% in COVID-19 female patients but were normal in COVID-19 male patients.

Conclusion: This study shows the role of other factors like previous intake of medications; other undiagnosed liver diseases should be established. However, the continue follow-ups and serial estimation of liver function test in COVID-19 affected patients are required to derive a conclusive evidence of chronicity of this viral liver disease.

Key words: Expectoration, Rhinorrheas, Severe acute respiratory syndrome coronavirus 2, Shortness of breath, Sore throat

INTRODUCTION

An outbreak of coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially started in December 2019 in the Wuhan province of china and on March 11, 2021, the World Health Organization declared COVID-19 as a global pandemic disease.[1] SARS-CoV-2 mainly affects the respiratory system.[2] Patients can experience a range of clinical manifestations, from no symptoms to critical illness. The common symptoms of COVID-19 are fever, cough, fatigue, shortness of breath, expectoration, rhinorrheas, sore throat, diarrhea, loss of smell and taste, etc. According to illness severity, SARS-CoV-2 infection was grouped into mild, moderate, and severe categories.[3,4] In SARS-CoV-2 infection, multi-organ involvement of heart, kidney, pancreas, and liver are reported.[5,6] Abnormal liver function test (LFT) results might be due to liver damage by SARS-CoV-2. Angiotensin-converting enzyme 2 receptor is expressed on cholangiocytes of liver as well as in the hepatocytes, but its expression is much higher in cholangiocytes which may act as potential gate of entry for the virus in the liver leading to dysregulation of liver function. SARS-CoV-2-induced hepatic damage can also be explained by immune mediated inflammation such as cytokine

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storm, pneumonia, associated hypoxia, hypotension, and drug hepatoxicity.[1,5] A study of postmortem liver biopsy in COVID-19 patient revealed moderate microvascular steatosis, mild lobular, and portal activity.[7,8] Multiple studies suggest that though mild derangements of liver function may be experienced by the most COVID-19 patients, but significant liver injury is not common. The effect of abnormal liver biochemistry of COVID-19 is still unclear. Some studies have found that there is a significant association between elevated aspartate transaminase (AST) and alanine transaminase (ALT) with disease severity and mortality, whereas other researchers did not find it.[1] Profoundly, a little data involving liver enzyme derangements and its clinical implications on the COVID-19 patients are available.

The major aim of study was to describe the clinical characteristics of COVID-19 patients admitted with moderate-to-severe pneumonia in the Government Medical College and Associated Hospital, Baramulla, and to find out their relation to the liver parameters.

MATERIALS AND METHODS

A descriptive cross-sectional study was conducted at Government Medical College Baramulla, from September 2021 to January 2022. The study proposal was approved by the Institutional Ethics Committee. The confirmed COVID-19 cases on the basis of RT-PCR of nasopharyngeal and oropharyngeal swab samples, admitted in dedicated COVID-19 ward during the period, were included in the study.[4] The moderate cases presented with features of fever, cough, dyspnea, hypoxia, (SpO_2 <94%), and respiratory rate of 24 or more. The patients with severe pneumonia or adult respiratory distress syndrome with SpO_2 <90% on room air, respiratory rate of more than 30 breaths per minute and chest X-ray infiltrates and occurrence of respiratory or other organ failure. The patients with underlying liver disease, including chronic hepatitis B and C, alcoholic or non-alcoholic fatty liver disease by less were excluded from the study. The patients with fever of any other infections' etiology such as malaria, dengue, and human immunodeficiency virus were excluded from study. Detailed medical history was taken from all the cases to assess the presence of comorbid complications in corona affected patients. Informed consent was taken and venous blood samples were collected aseptically in plain vials from each case after 12 h of fasting. Serum separated following centrifugation was analyzed using a biochemistry auto analyzer kenelsg. All samples were loaded and assayed in a blind fashion by an investigator who was unaware of participants clinical status in both study and catral groups. Serum levels of total bilirubin was estimated by Diazo method.[9] Liver enzymes ALT and AST were measured by IFCC method,[10] while alkaline phosphatase (ALP) level determination was done using AMP Buffer. Total protein and albumin were assayed using Biuret and Bromo cresol green reagents, respectively.[11] Statistical analysis was performed using BM statistical package for the social sciences. Software version 20 windows (IBM, New York USA) and inferences were drawn. All values were expressed as mean (+,−) standard deviation comparison of continuous variables between groups were evaluated using analysis of variance test. Categorical variables were compared using Pearson's Chi-squared test (χ^2) test.

RESULTS

The average baseline characteristics of the entire population are summarized in Table 1. Table 1 depicts the comparative status of LFT parameters in the study. Total bilirubin level was raised in the study population. The primary liver enzyme ALT was also raised in this study population. ALP and AST were also out of range. Serum total protein levels were out of their physiological limits in study population. Sr. Albumin level was also high. However, reduced serum globulin was observed. Out of 96 females, 6 (6.25%) patients were having elevated total bilirubin, 13 (13.54%) patients were having high total protein level, 1 (1.04%) patient was having high albumin level, 1 (1.04%) patient was having reduced globulin level, 14 (14.58%) patients were having high ALP levels, 8 (8.33%) patients were having high AST levels, and 12 (12.5%) patients were having high ALT levels. Out of 157 males, 26 (16.56%) patients were having elevated total bilirubin, 28 (17.83%) patients were having high total protein level, 9 (5.73%) patients were having high albumin level, all patients were having normal globulin level, 28 (17.83%) patients were having high ALP levels, 33 (21.02%) patients were having high AST levels, and 49 (31.21%) patients were having high ALT levels [Figures 1-7].

Table 1: Analysis of biochemical parameters of COVID-19 patients

Parameters	Average	SD
Total bilirubin	0.94 g/dL	0.6395
Total protein	7.87 g/dL	0.441
Albumin	4.99 g/L	2.557
Globulin	3.04 g/L	0.343
ALP	125.94 U/L	60.331
AST	37.86 U/L	22.34
ALT	48.49 U/L	37.79

ALP: Alkaline phosphatase, AST: Aspartate transaminase, ALT: Alanine transaminase

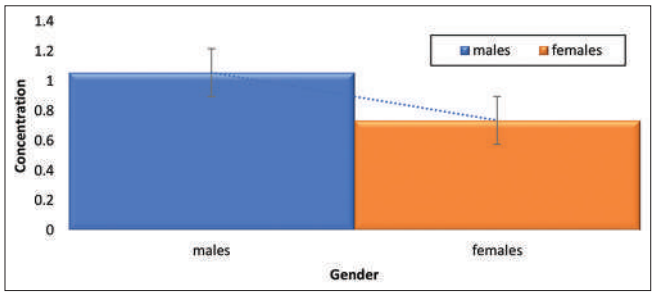

Figure 1: Average aspartate transaminase concentration in COVID-19 males and females

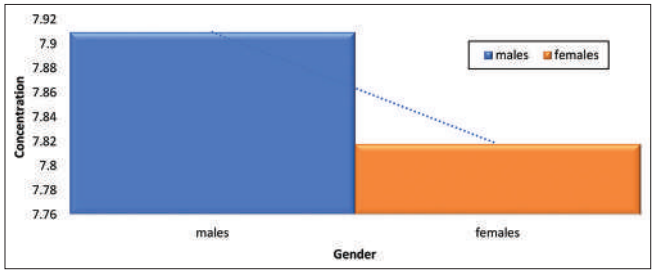

Figure 2: Average total protein concentration in COVID-19 males and females

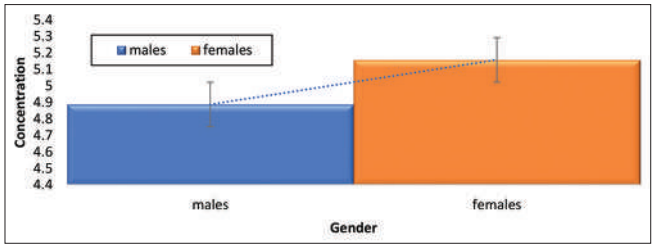

Figure 3: Average albumin concentration in COVID-19 males and females

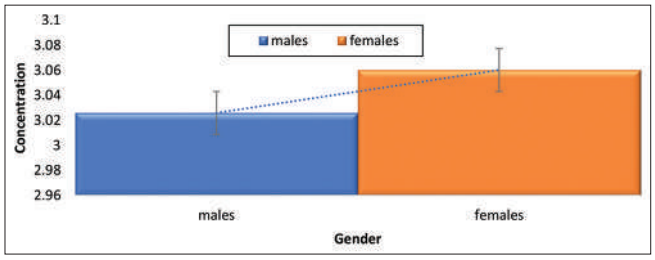

Figure 4: Average globulin concentratio in COVID-19 males and females

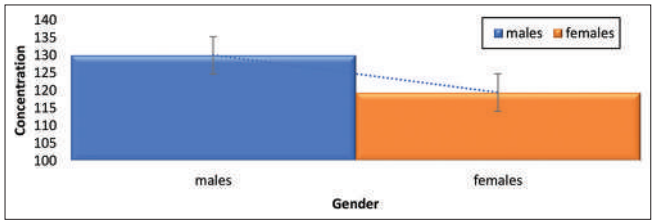

Figure 5: Average alkaline phosphatase concentration in COVID-19 males and females

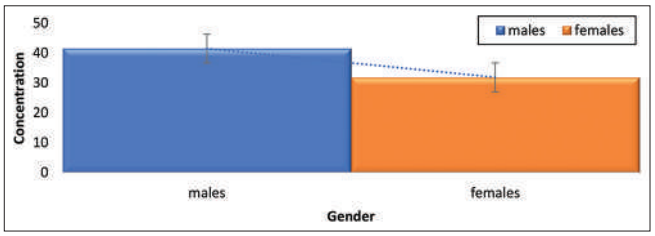

Figure 6: Average aspartate transaminase concentration in COVID-19 males and females

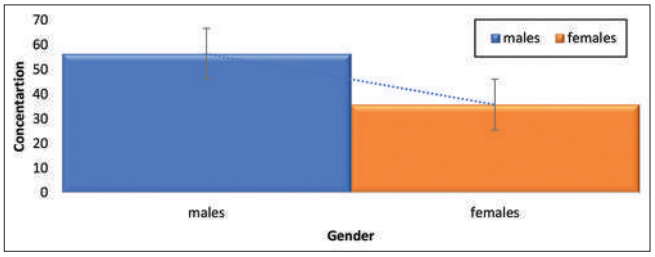

Figure 7: Average aspartate transaminase concentration in COVID-19 males and females

DISCUSSION

In patients admitted with COVID-19, liver dysfunction may be common. It is more in severe cases of COVID-19.[5,12] Abnormal liver enzymes in COVID-19 patients were first reported by (Chen *et al.*) from Wuhan. He had reported an increase in serum levels of ALT, AST, and lactate dehydrogenase in 43.4% of cases.[13] In a study from china, Average aspartate transaminase concentration in COVID-19 males and females it has been reported that there is higher elevation of ALT and AST in severe diseases (28.1%) compared to mild cases (19.8%).[14] Xu *et al.*, all in their recent study from Wuhan, found abnormal AST in severe cases (18.2%) and the incidence of liver injury in severe cases was also markedly higher (36.2%) than mild patients (9.6%).[15] Another study from Northern Italy revealed alteration of LFT in 62.4% of patients. In half of these patients, AST, ALT, and GGT were elevated, but reduced serum albumin levels were seen in 93.5% of cases.[16] The present study results are showing elevation of total bilirubin, total protein, ALT, AST, ALP, albumin levels, and reduced globulin levels. Elevated levels of ALT, AST, total bilirubin, total protein, albumin, and ALP were noted in 24.11%, 16.20%, 12.65%, 16.21%, 3.95%, and 16.60% and reduced level of Globulin was observed in 3.95% patients. The upper level of normal studies from South East Asia like those from Kaushik *et al.* in their study in Uttar Pradesh, India showed that 59.04% of admitted COVID-19 patients had abnormal LFT with elevated AST in 45.71% and elevated ALT in 25.21% cases.[17] A similar study from Palestine by (Asghar *et al.*) found elevated levels of liver enzymes, but they

had quoted significantly elevated levels of GGT and ALP, while, in contrast, we encountered normal levels of ALP with elevation of AST/ALT. The pathogenic mechanism of altered LFTs are not clear but most likely it seems multifactorial including hepatocytes and/or cholangiocyte infection, microthrombotic endothelialitis, immune dysregulation, drug-induced liver injury, and hepatic ischemic related to hypoxia and ICU related infections. The liver injury seems to be self-limiting and specific treatment is not necessary.[5,8] Abnormal LFT in COVID-19 is transient and simultaneously combined with increased enzymes from heart and muscle and it return to normal without any liver related morbidity and mortality.[13] Aminotransferase elevation in COVID-19 may be also due to myositis similar to severe influenza infection. A recent study had hypothesized that SARS-COV-2 binds directly to cholangiocytes demonstrating angiotensin-converting enzyme 2 (ACE) receptor and cause liver damage.[18] This explains partially the contribution of SARS-COV-2 infection to liver dysfunction in our patients.

Limitations

The limitation of this study is that the role of other factors like previous intake of medications, other undiagnosed liver diseases were not established. Continue follow-ups and serial estimation of LFT in COVID-19 affected patients is required to derive a conclusive evidence of chronicity of this viral liver disease.

CONCLUSION

Present study shows the role of other factors like previous intake of medications; other undiagnosed liver diseases should be established. However, the continued follow-ups and serial estimation of liver function test in COVID-19 affected patients are required to derive conclusive evidence of chronicity of this viral liver disease.

REFERENCES

1. Ridruejo E, Soza A. The liver in times of COVID-19: What hepatologists should know. Ann Hepatol 2020;19:353-8.
2. Weekly Epidemiological Update-17 November 2020 Data as Received by WHO from National Authorities, as of 10 am CEST 15 November 2020.
3. Centers for Disease Control and Prevention. Clinical Presentation of People with SARS-CoV-2 Infection. Available from: https://www.coronavirus.gov [Last accessed on 2020 Oct 09].
4. Government of India Ministry of Health and Family Welfare. Clinical Management Protocol: Covid-19. Version 3. Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division); 2020.
5. Ghoda A, Ghoda M. Liver injury in COVID-19 infection: A systematic review. Cureus 2020;12:e9487.
6. Bzeizi K, Abdulla M, Mohmmad N, Alqamish J, Jamshidi N, Broering D. Effect of COVID-19 on liver abnormalities: A systematic review and meta-analysis. Sci Rep 2021;11:10599.
7. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, *et al*. COVID-19 abnormal liver function tests. J Hepatol 2020;73:566-74.
8. Bertolini A, van de Peppel IP, Bodewes FA, Moshage H, Fantin A, Farinati F, *et al*. Abnormal liver function tests in patients with COVID-19: Relevance and potential pathogenesis. Hepatology 2020;72:1864-72.
9. Pearlman PC, Lee RT. Detection and measurement of total bilirubin in serum, with use of surfactants as solubilizing agents. Clin Chem 1974;20:447-53.
10. Thomas L. Alanine aminotransferase (ALT), Aspartate aminotransferase (AST). In: Thomas L, editor. Clinical Laboratory Diagnostics. Frankfurt am Main: TH-Books Verlagsgesellschaft; 1998.
11. Tietz NW, editor. Text Book of Clinical Chemistry. Philadelphia, PA: WB Saunders; 1986. p. 579-89.
12. Zhang C, Shi L, Wang FS. Liver injury in COVID-19 management and challenges. Lancet Gastroenterol Hepatol 2020;5:428-30.
13. Li J, Fan JG. Characteristics and mechanism of liver injury in 2019 coronavirus disease. J Clin Transl Hepatol 2020;8:13-7.
14. Guan W, Ni Z, Hu Y, Liang WH, Ou CQ, He JX, *et al*. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
15. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020; 40:998-1004.
16. Lenti MV, Andries FB, Pelligrino I, Klersy C, Merli S, Miceli E, *et al*. Impact of COVID-19 on liver function: Results from an internal medicine unit in Northern Italy. Intern Emerg Med 2020;15:1399-407.
17. Kaushik A, Wani SN, Baba MA, Agrawal AK. Prevalence of abnormal liver function tests in COVID-19 patients at a tertiary care centre. J Assoc Physicians India 2020;68:73-5.
18. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, *et al*. Specific ACE expression in cholangiocytes may cause liver damage after 2019-nCoV infection. Bio Rxiv 2020;2020-02.

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Original Article

Costoclavicular versus Lateral Sagittal Approach of Infraclavicular Brachial Plexus Block for Upper Limb Surgeries: A Prospective Comparative Study

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Abstract

Background and Aim: The infraclavicular brachial plexus blocks are an alternative to axillary block for anaesthetizing elbow, forearm, and hand surgeries. Furthermore, they are associated with lesser complication rates as compared to supraclavicular blocks. Hence, this study is undertaken to compare two approaches of infraclavicular brachial plexus block with respect to block hemodynamics.

Methodology: This prospective and comparative study was done in 40 patients posted for the upper limb surgeries for a duration of 2 months under American Society of Anesthesiologists I, II, III. Here patients will be divided into two groups randomly. First group will receive lateral sagittal approach infraclavicular brachial plexus block with 20 mL of 0.5% Bupivacaine and second group will receive costoclavicular approach of infraclavicular brachial plexus block with 20 mL of 0.5% Bupivacaine. Block performance time and dynamics are compared between two groups.

Outcome Measures: To assess Imaging time, needling time, block performance time, number of needle redirections, onset of sensory and motor block**,** duration of block, duration of surgery, surgeon and patient satisfaction score, number of patients who require a rescue block, and complications associated with block.

Results: Imaging time, Needling time, block performance time, and number of needle redirections are lesser in costoclavicular approach as compared to lateral sagittal approach. None of the patients required any rescue blocks in both the groups. No complications were noted in both the groups.

Conclusion: Costoclavicular approach is easy to perform in terms of block performance as cords are clustered at a single anatomical location as compared to lateral sagittal approach.

Key words: Brachial plexus block, Costoclavicular, Lateral sagittal, Upper limb surgeries

INTRODUCTION

Peripheral nerve blocks are a type of locoregional anesthesia that provides a targeted and localized anesthesia of extremities both for surgical anesthesia and post-operative analgesia. It has more advantages in that anesthesia is provided to a particular area of interest and general systemic side effects of polypharmacy are avoided. Furthermore, it is a part of multimodal analgesia in this upcoming era of opioid free anesthesia. Brachial plexus block is used to anaesthetize upper limb for surgeries involving from shoulder to fingertips. Various approaches are available to block brachial plexus which include – interscalene block, superior trunk block, supraclavicular brachial plexus block, infraclavicular brachial plexus block, and axillary block. The brachial plexus is formed by the nerve roots from C8 to T1. The nerve roots split to form superior, middle, and inferior trunks above the clavicle. As the trunks pass under the clavicle, it is found in close proximity with each other and it is easier to block at this level. Below the clavicle, the brachial plexus splits to form

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the lateral, medial, and posterior cords around the axillary artery. The infraclavicular brachial plexus block provides anesthesia and analgesia from mid-humerus to finger tips.[1] The infraclavicular brachial plexus blocks are an alternative to axillary block for anaesthetizing the elbow, forearm, and hand surgeries. Infraclavicular brachial plexus block was developed to overcome the limitations of axillary block which includes musculocutaneous nerve sparing. Furthermore, infraclavicular block has several advantages that make it a preferable approach to brachial plexus blockade: Comprehensive upper extremity anesthesia, lower incidence of tourniquet pain, and preferable site for catheter insertion. Our main objective was to compare the block performance and block dynamics in terms of imaging time, needling time, block performance time, number of needle redirections, onset of sensory, and motor blockade. Hence, this study is undertaken to compare two approaches of infraclavicular brachial plexus block with respect to block hemodynamics.

METHODOLOGY

This was a prospective and comparative study conducted in a tertiary care hospital of South India in the setting of operation theater complex and post-anesthesia care unit for a study duration of 2 months among patients posted for upper limb surgeries. This study is done after getting Institutional Ethical Committee clearance in accordance with declaration of Helsinki. Each patient was given informed consent form explaining the procedure, drugs used, risks, and benefits. Patients between age group of 18 years to 80 years, those scheduled for elective forearm and hand surgeries, and patients with American Society of anesthesiologists (ASA) 1–3 are included in this study. Patients not consenting/unwilling to participate, age <18 years or >80 years. Patients with ASA 4, obesity (BMI >30 kg/m^2), those with contraindications to regional anesthesia (thrombocytopenia and infection at injection site), history of hypersensitivity or allergy to local anesthetics, and those patients requiring conversion to general anesthesia are excluded from this study. Group size of 20 was calculated using power analysis from a previous study report. The upper limb surgeries included are forearm fractures, hand surgeries, and AV fistula creation in end stage renal disease patients requiring hemodialysis. Continuous sampling was done and our study included 40 patients, out of which 20 patients were given lateral sagittal approach of infraclavicular brachial plexus block (Group LS) and rest were given costoclavicular approach of infraclavicular brachial plexus block (Group CC). Our primary objectives are to assess imaging time (time from placement of USG probe to proper visualisation of cord along with axillary artery), to assess needling time (time from needle insertion to needle out time after deposition of local anesthetic), to assess block performance time

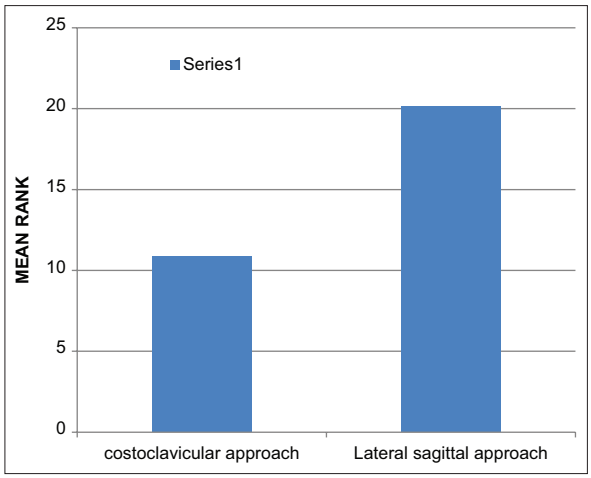

Figure 1: Bar graph showing comparison of imaging time among both the groups

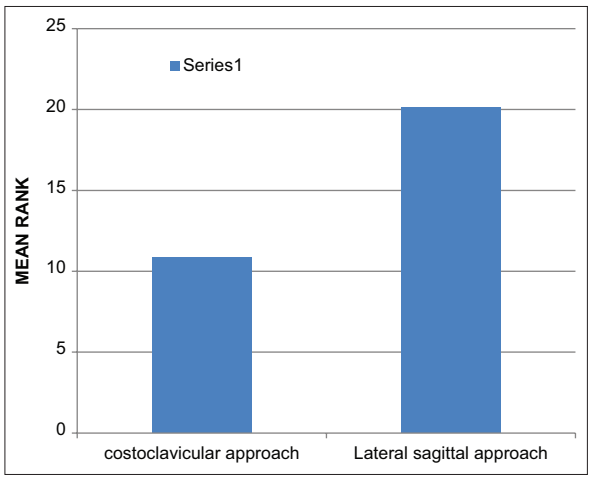

Figure 2: Bar grouph showing needling time comparison among both the groups

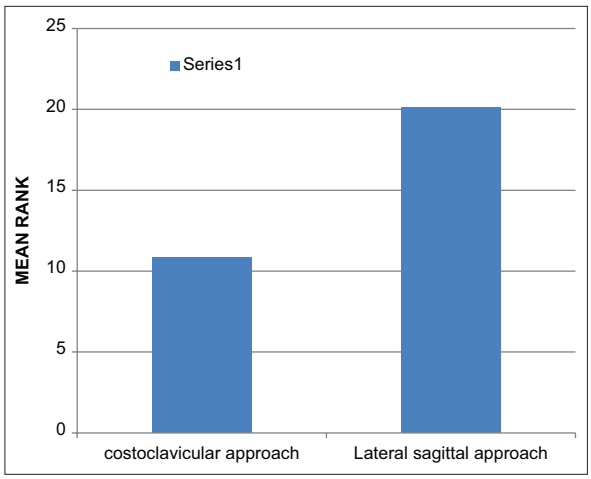

Figure 3: Bar graph showing block performance time comparison among both the groups

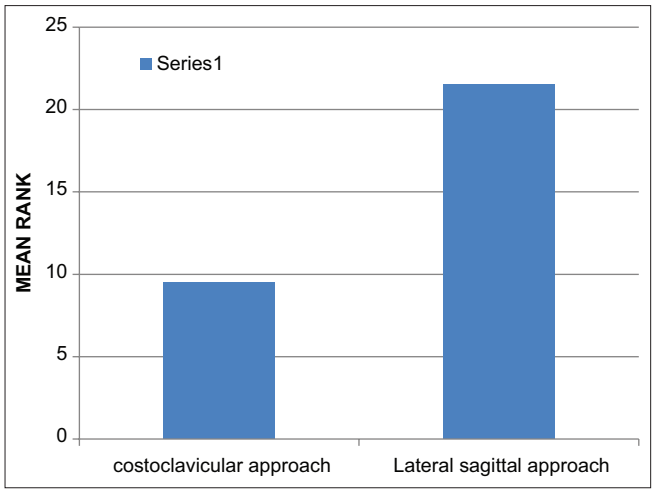

Figure 4: Bar graph showing Number of needle redirections comparison among both the groups

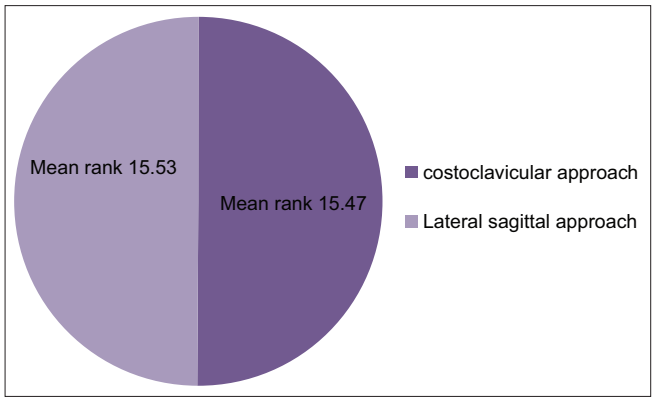

Figure 5: Pie chart showing comparison of onset of sensory block among both the groups

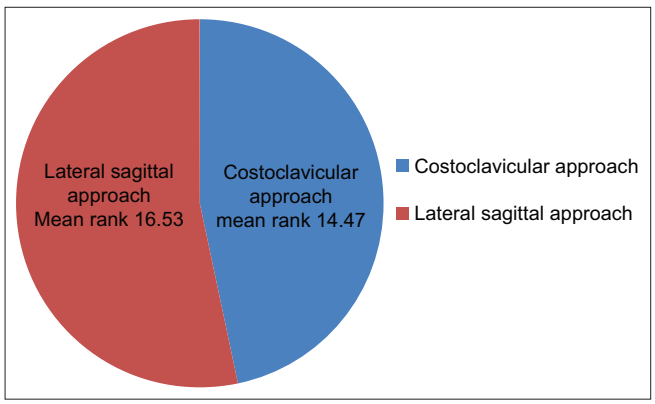

Figure 6: Pie chart showing onset of motor block comparison among both the groups

(imaging time + needling time), to assess number of needle redirections, and to assess the onset of sensory and motor block. Secondary objectives are to assess the duration of analgesia, number of patients who require a rescue block, and complications associated with block. All the patients in both the groups received the same treatment protocol.

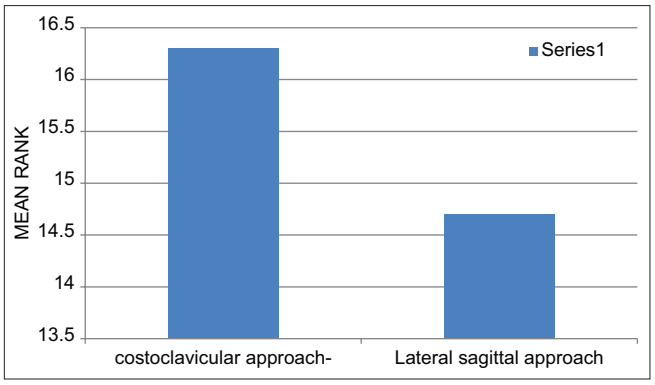

Figure 7: Bar graph showing comparison of duration of analgesia among both the groups

All patients were pre-medicated with 0.1 mg/kg midazolam intravenously. Routine monitoring includes electrocardiogram, pulse oximetry, and non-invasive blood pressure. Supplemental oxygen was administered through oxygen mask at a flow rate of 4 L/min.

Site of intervention was painted and drained under sterile aseptic precautions. All blocks were performed under ultrasound guidance ("Sonosite") using high frequency linear probe with the patient in supine position and head turned toward opposite side. In lateral sagittal approach, the sterile ultrasound probe was placed medial to the coracoid process in the sagittal plane in the infraclavicular region, and then three cords of the brachial plexus were visualized [Figure 8]. Furthermore, the major vascular bundles axillary artery and axillary vein are visualized. Using 23G spinal needle and by the in-plane technique needle is directed in a craniocaudal direction and 20 mL of bupivacaine 0.5% will be administered around the posterior cord (7 mL), lateral cord (7 mL), and medial cord (6 mL) [Figure 11].

In costoclavicular approach, patient was positioned in supine position with head rotated toward opposite side away from site of surgery with arms abducted at an angle of 90°. The sterile ultrasound probe was placed parallel to the clavicle in the midclavicular area and tilted toward the cephalad and the axillary artery, and three cords were visualized [Figure 9]. A 23G spinal needle was forwarded from lateral to medial using the in-plane technique, and 20 mL of bupivacaine 0.5% was administered at the center of the three cords in the costoclavicular space [Figure 10].

Adequacy of blocks was checked using pinprick sensation along the dermatomal distribution of ulnar nerve, median nerve, and radial nerve after about 15 to 20 min of local anesthetic injection and before the commencement of surgery. Furthermore, any dermatomal sparing requiring rescue blocks were assessed.

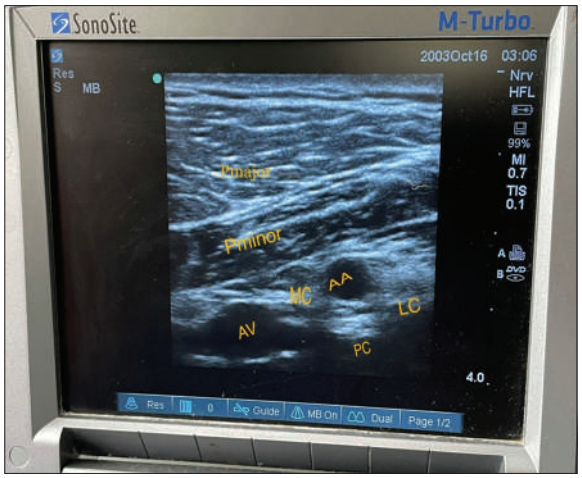

Figure 8: Image showing sonoanatomy of lateral sagittal approach of infraclavicular brachial plexus block
Pmajor: Pectoralis major, Pminor: Pectoralis minor, AV: Axillary vein, AA: Axillary artery, PC: Posterior cord, MC: Medial cord, LC: Lateral cord

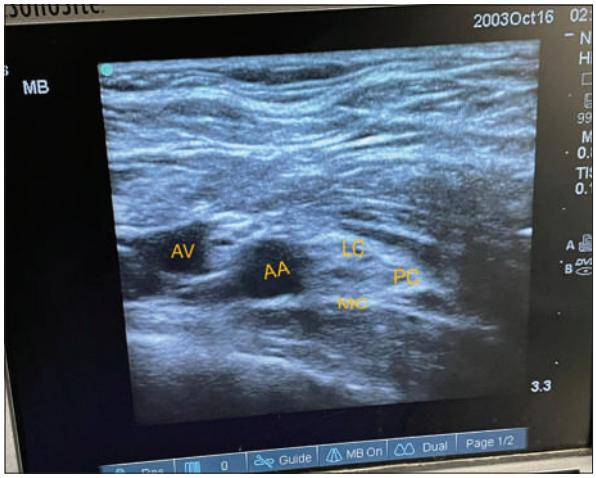

Figure 9: Image showing sonoanatomy of costoclavicular approach of infraclavicular brachial plexus block
AV: Axillary vein, AA: Axillary artery, PC: Posterior cord, MC: Medial cord, LC: Lateral cord

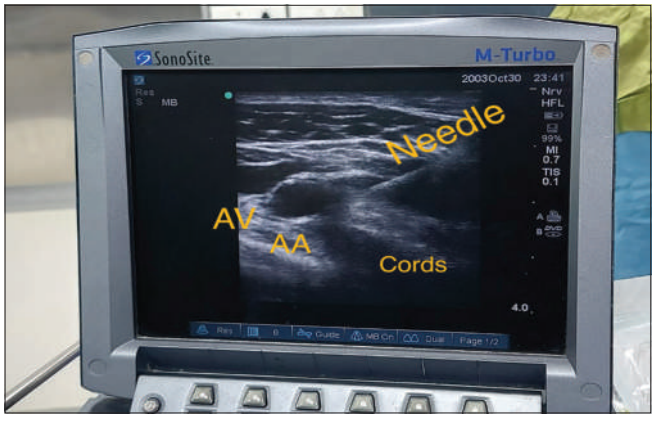

Figure 10: Image showing needle position in costoclavicular approach of infraclavicular brachial plexus block

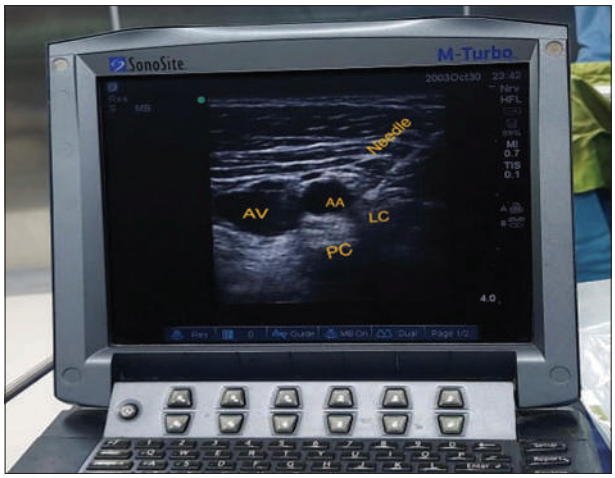

Figure 11: Image showing needle position in lateral sagittal approach of infraclavicular brachial plexus block

Block performance time and block dynamics were assessed and compared with both the groups in terms of imaging time, needling time, block performance time, number of needle directions, onset of sensory, and motor blockade. None of the patients were sedated intraoperatively. Hemodynamic monitoring was done intraoperatively for both the groups. Need for rescue analgesia was also assessed and recorded. Both the groups were monitored for block complications such as pneumothorax, accidental vascular puncture, local anesthetic toxicity, Horner's syndrome, and local site hematoma. Postoperatively patient was monitored in the recovery room and shifted to ward with an Aldrete score >9.

Statistical analysis of continuous variables such as imaging time, needling time, block performance time, no. of needle redirections, onset of sensory, and motor block was done using Mann–Whitney U test. A confidence interval of 95% was used in all statistical tests and $P < 0.05$ is considered to be statistically significant.

RESULTS

The imaging time was higher in the lateral sagittal approach infraclavicular brachial plexus group with a mean rank of 20.13 versus 10.87 (s) in the costoclavicular approach infraclavicular brachial plexus group and was statistically significant with $P = 0.004$ [Table 1 and Figure 1]. Furthermore, the needling time was higher in the Group LS mean rank of 19.47 versus 11.53 in the Group CC (seconds) but was not statistically significant [Figure 2]. Moreover, the block performance time was statistically significantly longer in the Group LS as compared to Group CC 20.43 versus 10.57 (s) with $P = 0.002$ [Figure 3]. The number of needle directions that were higher in the Group LS

Table 1: Results showing statistical analysis of block performance and dynamics

Parameters	Costoclavicular approach (mean rank)	Lateral sagittal approach (mean rank)	*P*-value
Imaging time	10.87	20.13	0.004
Needling time	11.53	19.47	0.13
Block performance time	10.57	20.43	0.002
No. of needle redirections	9.50	21.50	0.001
Onset of sensory block	15.53	15.47	0.982
Onset of motor block	14.47	16.53	0.509
Duration of analgesia	16.30	14.70	0.614

with a mean rank of 21.50 and was statistically significant [Figure 4]. Furthermore, the block was successful in all patients and the onset of sensory block was similar in both the groups and was not statistically significant (P = 0.98) [Figure 5]. Furthermore, the onset of motor block was earlier in Group CC with a mean rank 14.47 (min) versus Group LS with a mean rank of 16.53 (min) but was not statistically significant [Figure 6]. Duration of analgesia was higher in Group CC but was not statistically significant (P = 0.61) [Figure 7]. Moreover, none of the patients required any rescue blocks or conversion to general anesthesia. No complications were encountered in both the groups such as vascular puncture, local site hematoma, pneumothorax, local anesthetic toxicity, horners syndrome, or any neurological complications.

DISCUSSION

Our present study shows that imaging and block performance time were longer in the lateral sagittal approach of infraclavicular brachial plexus block. However, there was no significant difference in the onset of sensory and motor block. One of the contemporary technological advances in the field of anesthesia is the introduction of anatomical evaluation by ultrasound imaging. Widespread use of ultrasound imaging depends on its proven clinical efficacy, cost effectiveness, and practicality as it provides anesthesiologist the visual treat to evaluate complex and varied anatomy of the local structures before needle insertion.

In costoclavicular approach, the cords are located at a more superficial level and clustered lateral to axillary artery at a depth of 3–4 cm whereas in lateral sagittal approach, the cords are in deeper level (4–5 cm) and are separated from one another around the artery.[2] This explains the greater imaging time and block performance time of lateral sagittal approach as compared to costoclavicular approach in our study. Furthermore, the greater number of needle redirections in the lateral sagittal approach can be explained by the anatomical arrangement of cords around the axillary artery along the 3, 6, and 9 o clock positions whereas in the costoclavicular approach, the cords are clustered lateral to the axillary artery.[3]

A randomized study by Yayik *et al.* in 60 pediatric patients undergoing forearm and hand surgeries found that needling time and block performance time was significantly longer in lateral sagittal group as compared to costoclavicular group. Moreover, there was no significant difference in the imaging time, number of needle passes, onset of sensory, and motor block.[4]

Few studies by Dingemans *et al.* and Gurkan *et al.* showed reduced block performance time and equal success rate with the use of ultrasound guidance alone rather than ultrasound with neurostimulation technique.[5,6]

A study by Monzó *et al.* on microanatomical considerations of brachial plexus block in the costoclavicular region found that there was interplexus fascial septum that separates the lateral cord from the posterior and medial cords in 94% of population which suggests that two separate injections are needed to block the cords to ensure adequate local anesthetic spread.[7]

Onset of sensory block showed no difference among both the groups in our study whereas costoclavicular approach showed a faster onset of motor block compared to lateral sagittal approach but was not statistically significant. Later onset of motor block in lateral sagittal approach may be due to the individual anatomical variations, depth of the cords, and the distance between them.

A RCT by Leurcharusmee *et al.* among 90 patients posted for upper limb surgeries using 35 mL mixture of 1% of lignocaine with 0.25% of bupivacaine and adrenaline 5 mcg/mL showed that there were no significant intergroup differences in terms of block performance time. However, the number the needle passes were marginally fewer in the lateral sagittal approach as compared to costoclavicular approach.[8]

A study by Li *et al.* in 40 patients undergoing elective upper extremity surgery using 25 mL of 0.5% of ropivacaine found that the onset of sensory block was faster in costoclavicular approach as compared to lateral sagittal approach (10 min vs. 20 min) and P = 0.004.[9]

Moreover, none of the patients in our study required any rescue block or had any complications associated with

the block. The amount of local anesthetic used can be reduced by ultrasound guidance and proper visualization of the cords which is an added advantage. A study by Wong *et al.* in 40 patients undergoing elective forearm and hand surgeries found that the minimum effective local anesthetic volume of 0.5% ropivacaine was found to be 20.9 mL. Furthermore, there are only very few literatures available for this infraclavicular approaches.[10]

There are few limitations in our study. First, the sample size is limited. Surgeon satisfaction score was not assessed at the end of the procedure which could have guided better in comparing both the approaches. More studies are encouraged in the near future to provide a comprehensive data for analysis leaving the fear of complications of pneumothorax while performing infraclavicular brachial plexus block which can be avoided under ultrasound guidance. Furthermore, there are few literatures available with regard to infraclavicular approach.

CONCLUSION

Costoclavicular approach is easy to perform in terms of block performance as cords are clustered at a single anatomical location as compared to lateral sagittal approach with maximum success rate and minimum complications.

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REFERENCES

1. Pester JM, Hendrix JM, Varacallo M. Brachial plexus block techniques. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022.
2. Sala-Blanch X, Reina MA, Pangthipampai P, Karmakar MK. Anatomic basis for brachial plexus block at the costoclavicular space: A cadaver anatomic study. Reg Anesth Pain Med 2016;41:387-91.
3. Dost B, Kaya C, Ustun YB, Turunc E, Baris S. Lateral sagittal versus costoclavicular approaches for ultrasound-guided infraclavicular brachial plexus block: A comparison of block dynamics through a randomized clinical trial. Cureus 2021;13:e14129.
4. Yayik AM, Cesur S, Ozturk F, Celik EC, Naldan ME, Ahiskalioglu A. Comparison of the lateral sagittal and costoclavicular approaches for ultrasound-guided infraclavicular block in pediatric patients: A prospective randomized study. Braz J Anesthesiol 2021;S0104-0014(21)00224-4.
5. Dingemans E, Williams SR, Arcand G, Chouinard P, Harris P, Ruel M, *et al*. Neurostimulation in ultrasound-guided infraclavicular block: A prospective randomized trial. Anesth Analg 2007;104:1275-80.
6. Gurkan Y, Tekin M, Acar S, Solak M, Toker K. Is nerve stimulation needed during an ultrasound-guided lateral sagittal infraclavicular block? Acta Anaesthesiol Scand 2010;54:403-7.
7. Monzó E, Boezaart AP, Tubbs RS, Sanromán-Junquera M, Nin OC, Reina MA. A reliable septum exists between the lateral cord and medial and posterior cords in the costoclavicular region: Clinical and microanatomical considerations in brachial plexus anesthetic blockade. Clin Anat 2021;34:411-9.
8. Leurcharusmee P, Elgueta MF, Tiyaprasertkul W, Sotthisopha T, Samerchua A, Gordon A, *et al*. A randomized comparison between costoclavicular and paracoracoid ultrasound-guided infraclavicular block for upper limb surgery. Can J Anaesth 2017;64:617-25.
9. Li JW, Songthamwat B, Samy W, Sala-Blanch X, Karmakar MK. Ultrasound-guided costoclavicular brachial plexus block: Sonoanatomy, technique, and block dynamics. Reg Anesth Pain Med 2017;42:233-40.
10. Wong MH, Karmakar MK, Mok LY, Songthamwat B, Samy W. Minimum effective volume of 0.5% ropivacaine for ultrasound-guided costoclavicular brachial plexus block: A dose finding study. Eur J Anaesthesiol 2020;37:780-6.

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Original Article

Role of Saliva in Diagnosis and Estimation of Disease Severity in Pemphigus Vulgaris using Autoantibody Levels: A Comparative Study between Serum and Saliva

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Abstract

Introduction: While studies abound on estimation of anti-desmoglein-1,3 autoantibodies in serum of Pemphigus vulgaris patients, there is scarcity of literature investigating their levels in saliva and their correlation with severity of disease.

Purpose: The aim of present study was to estimate and compare the correlations of levels of serum and salivary anti-Dsg-1, anti-Dsg-3 antibodies, and disease severity according to the standardized index of measuring severity of disease, that is, Pemphigus disease area index (PDAI). Furthermore, we attempted to find out correlation, if any, between salivary anti-Dsg-1, anti-Dsg-3 antibodies, and oral mucosal disease severity by including oral mucosal component of PDAI, which is hitherto unexplored in the studies so far.

Materials and Methods: Autoantibodies against desmoglein-1,3 were assayed by Enzyme-linked immunosorbent assays in serum and saliva samples of patients and healthy controls.

Results: Titers of serum and salivary anti-Dsg-1, anti-Dsg-3 significantly correlated with overall disease severity. In addition, the titers of both Abs in saliva showed a statistically significant correlation with oral disease severity, much like its serum counterpart.

Conclusion: Our results indicate that salivary biofluid has tremendous potential to be used for diagnosis and monitoring disease activity in Pemphigus vulgaris patients and merits further studies.

Key words: Pemphigus, Saliva, Serum, Enzyme-linked immunosorbent assays, Autoantibodies

INTRODUCTION

The term Pemphigus derived from the Greek word "Pemphix" (bubble or blister) is used to describe a group of potentially life-threatening autoimmune mucocutaneous diseases characterized by epithelial blistering, on cutaneous and/or mucosal surfaces afflicting skin, scalp, nails, and also the mucosae of the mouth, nose, conjunctivae, genitals, esophagus, pharynx, and larynx.[1]

Of the various forms of pemphigus, pemphigus vulgaris is the most common, potentially fatal tissue specific autoimmune disease primarily afflicting the mucous membranes, predominantly the oral cavity.[2,3] At the cellular level, the defect lies in interruption of the proper intercellular adhesion in the epidermis and mucous

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membranes, by targeting glycoprotein components of desmosomal adhesion molecules, that is, desmoglein-1 (Dsg-1) and desmoglein-3 (Dsg-3) resulting in a loss of cell-to-cell attachment, that is, acantholysis with intraepithelial split formation. This clinically transcends into appearance of very fragile blisters that rupture leaving erosions, which affect either or both the mucosa and the skin resulting in three distinct clinical phenotypes: Mucosal, cutaneous, or mucocutaneous polycythemia vera (PV).[4,5] Oral manifestations constitute an important aspect of PV since often they are the initial presenting features or in some cases the only symptom of the disease.[6,7]

Conventionally, the diagnosis of PV is based on the histopathologic evaluation of skin or mucosal biopsies showing characteristic suprabasal clefting and acantholytic cells, which are confirmed by the demonstration of immunoglobulin G (IgG) and complements deposition on the direct immunofluorescence (DIF) staining of the perilesional normal skin. Beautner and Jordan demonstrated circulating immunoglobulin G (IgG) antibodies reactive against Dsg-3 and Dsg-1 in the serum of PV Patients which can be detected and quantified by Indirect immunofluorescence (IIF).[8] Further studies elucidated that the antibody titer in serum reflect disease activity and could be used to monitor therapeutic response.[5,9] For the past decade, enzyme-linked immunosorbent assays (ELISA) using recombinant desmogleins 1 (Dsg1) and 3 (Dsg3) have emerged as a promising, more sensitive and specific method enabling quantitative measurement of these autoantibody levels and several studies have extensively documented the presence of IgG antibodies against Dsg Ags by serum ELISA assay. At present, there is a growing endeavor to establish non-invasive methods of diagnosis. In this context saliva as a biofluid has shown tremendous promise due to its ease of handling, possibility of repeated sampling, being patient friendly and unlike serum it is devoid of coagulation issues. This has provided much impetus to the use of saliva as a potential diagnostic biological tool in various diseases such as Sjogren's syndrome, cystic fibrosis, diabetes mellitus, and HIV. As such, ELISA using saliva as the biofluid substrate, instead of blood serum, has been proposed as a noninvasive, rapid, and convenient method for the diagnosis of autoimmune disorders, including PV.[3,10-14] However, the use of salivary ELISA for diagnostic purpose in PV has not been extensively studied.[6] Furthermore, there is dearth of literature highlighting the impact of autoantibody titers in saliva on the severity of oral and cutaneous lesions.

The aim of the present study is to evaluate the diagnostic value of Dsg ELISA in PV patients by investigating the correlation between serum and salivary anti-Dsg1, anti-Dsg3 antibodies, and disease severity according to the standardized index of measuring severity of disease, that is, pemphigus disease area index (PDAI).

In addition, we attempted to find out correlation, if any, between saliva anti-Dsg1, anti-Dsg3 antibodies, and oral mucosal disease severity by including oral mucosal component of PDAI (OMPDAI). To the best of our best knowledge, this is the first study to highlight the correlation between anti-Dsg titers and severity of oral disease in PV. Simultaneously assessments were made whether the correlations between salivary antibody levels and disease severity tend to parallel those between serum antibody levels and disease severity, to establish the accuracy of saliva as a diagnostic alternative to serum.

MATERIALS AND METHODS

Thirty untreated patients with Pemphigus Vulgaris presenting to the Department of Skin and V.D., S.C.B. Medical College and Hospital, and SCB Dental College and Hospital, Cuttack, were voluntarily enrolled into the study. The diagnosis of the disease was based on histopathology and direct immunofluorescence findings in favor of PV. Demographic data including gender and age were recorded on a predesigned questionnaire. Clinical characteristics of the disease including the phenotype of disease, namely, cutaneous, mucosal, and mucocutaneous, were recorded as well. Scoring of the disease based on the PDAI was also recorded. Tto compare the patients with an appropriate pemphigus-free control group, 20 age- and sex-matched individuals, clinically free of any autoimmune disease based on their medical history and physical examination were also recruited into the study.

Ethical Standard

The study was conducted with prior approval and clearance from Institutional ethical committee, SCB Dental College and Hospital, Cuttack under the required norms and regulations. (IEC/SCBDCH/011/28/12/2018).

Human Serum and Saliva Samples

Collection of serum sample was done by the method recommended by National Institute of Health (NIH-Bethesda, MD, USA, 2009). Five milliliters of blood sample were drawn from the antecubital vein of each participant under aseptic conditions and collected in disposable, non-pyrogenic, and non-endotoxin blood collection tubes. The samples were allowed to remain for 2 h at room temperature to allow sedimentation of cellular fraction of blood. Later, sedimented blood sample was centrifuged for 20 min at approximately 1000× g. The supernatant serum was separated out with the help of micro-pipette in sterile microcentrifuge tubes and stored in −70°C.

For collection of saliva samples, the patients were instructed to collect unstimulated whole saliva in their oral cavity for 5 min without swallowing and then told to spit it into sterile disposable plastic containers. Care was taken to see that the patients did not consume food, drinks or smoke at least 1 h before the saliva collection procedure. Then, the supernatants of the salivary samples were separated by centrifugation at 1000 g for 20 min and collected in sterile microcentrifuge tubes and stored in −70°C. In order to prevent circadian variations, the serum and saliva samples were obtained from 9:00 to 11:00 AM. All the pemphigus patients had the typical clinical oral and skin lesions [Figure 1a and b], histological [Figure 2a] and immunopathological (direct immunofluorescence, Figure 2b) findings, of PV and the serum/saliva samples were collected when these diseases were active.

Anti-Dsg1 and Anti-Dsg3 ELISA

Anti-Dsg1 and anti-Dsg3 ELISA were performed on both the serum and the salivary samples using the EUROIMMUN (Medizinische Labordiagnostika AG, Germany) kit according to previous studies and the manufacturer's instructions for conducting serum ELISA. Anti-Dsg 1 and anti-Dsg 3 ELISA were performed on the serum samples which were diluted to (1/100) in accordance with the manufacturer instructions. For serum anti-Dsg1 and anti-Dsg3 ELISA, the standard manufacturer's recommended cutoff value of 20.0 RU/mL was used. The dilution of salivary samples prepared for ELISA in a previous study was not clearly stated; 15; moreover, we reached acceptable results from non-diluted salivary samples. Therefore, we used non-diluted salivary samples in our study. Since the kit had been specifically designed for serum anti-Dsg1 and anti-Dsg3 measurements, the results of saliva samples were evaluated using the optimized cut-off values based on the previous studies (7.7 RU/mL and13.4 RU/mL for the salivary anti-Dsg1 and anti-Dsg3 ELISA, respectively). According to these studies, different cutoff values were used to provide more reliable results. All procedures were performed according to the manufacturer's recommendation.

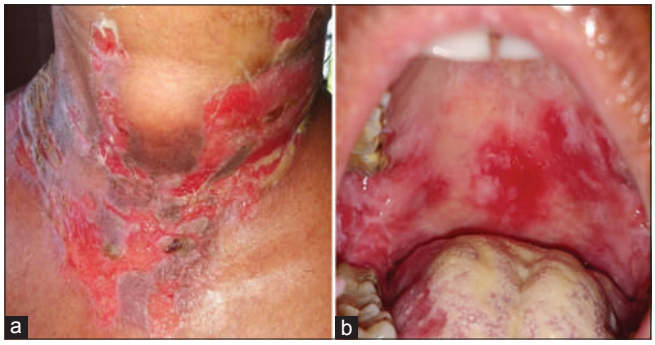

Figure 1: (a) Extensive denuded surface of skin due to detachment of epidermis following rupture of blisters with crust formation. (b) Multiple persistent oral erosions and ulcers in the oral cavity of polycythemia vera patients. These were preceded by blisters that readily ruptured due to oral trauma

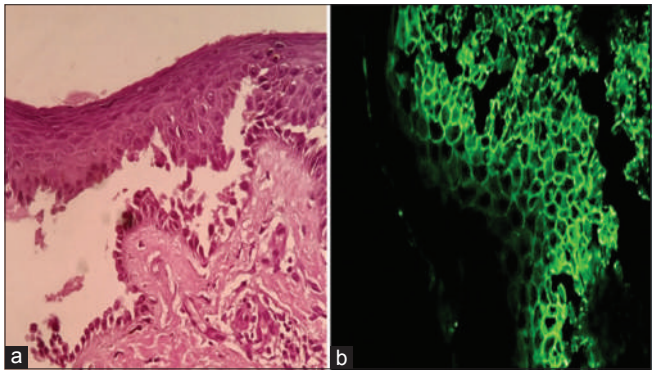

Figure 2: (a) Histopathologic examination of mucosal lesion biopsy revealed supra-basilar split with separation of overlying epithelium and residual basal keratinocytes at the basement membrane zone, producing a "tombstone effect." (b) Direct immunofluorescence perilesional area revealed an intercellular staining of IgG antibodies giving rise to a "chicken wire pattern."

Statistical Analysis

Statistical analysis of the data was performed using the IBM SPSS Statistics software (version 21.0; IBM Corp., Armonk, NY, USA) for Microsoft Windows. The Spearman's (rs) correlation coefficient was used to investigate correlation between anti-Dsg 1and anti-Dsg 3 in serum and saliva and their correlation with the disease severity. $P < 0.01$ was considered statistically significant.

RESULTS

The study involved a total of 50 subjects, out of which 30 were Pemphigus Vulgaris patients and 20 were healthy controls. Among the 30 diseased cases, 13 were males and 17 females while the control group comprised 7 males and 13 females. The mean age in PV patients was 48.3 ± 10.21 while in healthy controls it was 43.95 ± 10.45.

Raised Serum and Salivary Anti-Dsgs in PV Patients

The findings of this study showed that mean titers of anti-Dsg-1 and 3 Abs in both serum and saliva of PV patients were significantly greater than those found in healthy controls using unpaired t test [Table 1].

For Anti-Dsg 1 93.33%, patients were positive for serum antibodies while the same Abs in saliva were found to be present in 83.33% patients. As regard Anti-Dsg-3 96.66%, PV patients were positive for Abs in serum, in contrast 86.66% patients had anti-Dsg-3 Abs in saliva. In our study, we have found mean levels of Anti-Dsg-3 to be greater than mean levels anti-Dsg-1 in both serum and saliva.

Table 1: Summary of data for Dsg-1 and Dsg-3 ELISA in serum and saliva of PV patients and healthy controls

Group	Anti-Dsg-1 Abs		Anti-Dsg-3 Abs	
	Serum (mean±SD*)	Saliva (mean±SD*)	Serum (mean±SD*)	Saliva (mean±SD*)
Cases (*n*=30)	155.66±87.23	17.21±10.27	181.76±102.95	25.12±13.10
Controls (*n*=20)	1.5±0.94	1.42±0.94	1.49±0.80	1.11±0.65

*Standard deviation

Correlation of Serum and Salivary Anti-Dsg Antibodies

There was statistically significant correlation between serum anti-Dsg titers with their salivary levels. Good correlation was found between serum and salivary anti-Dsg-1 levels (r = 0.897, *P* = 0.000) while a stronger positive correlation was obtained between serum and salivary anti-Dsg-3 levels (r = 0.964, *P* = 0.000) [Table 2].

Correlation of Serum and Salivary Anti-Dsg Values with Pemphigus Score (PDAI)

Total and oral disease severity in PV patients was studied using Total PDAI score and OMPDAI score, respectively. PDAI was calculated for each patient by two independent observers. The results were analyzed using "kappa" statistics as a measure of inter observer agreement and excellent agreement values of 0.896 and 0.893 were obtained for both total PDAI and OMPDAI, respectively.

Individual correlations of mean titers of anti-Dsg-1, Anti-Dsg-3 Abs in saliva with each of the two severity scores, that is, total PDAI and OMPDAI were made using Spearman's correlation coefficient and these were compared with similar correlations using mean Ab titers in serum [Table 3].

As per our findings, salivary Anti-Dsg-1 levels showed statistically significant correlation with total PDAI as well as OMPDAI scores (*r* = 0.831, 0.725 respectively; *P* = 0.001 for each) [Figure 3c and d]. Drawing comparison with the serum counterpart, serum Anti-Dsg-1 titers also showed statistically significant but stronger correlation with total PDAI and OMPDAI (*r* = 0.933, 0.756 respectively; *P* = 0.001 for each) [Figure 3a and b].

As compared to salivary anti-Dsg-1 levels, the anti-Dsg-3 Ab levels in saliva showed a stronger statistically significant correlation with total disease severity (PDAI; *r* = 0.903) [Figure 4c] as well as oral mucosal disease severity (OMPDAI; *r* = 0.754) [Figure 4d] with p value=0.001 for both correlations. Interestingly, this stronger correlation of anti-Dsg 3 Abs compared to anti-Dsg-1 as obtained in saliva, was also closely simulated by the serum titers of anti-Dsg-3 (*r* = 0.948 for total PDAI; *r* = 0.762 for OMPDAI; *P* = 0.001 for each) [Figure 4a and b] showing a stronger positive correlation than anti-Dsg-1 in serum.

Table 2: Correlation coefficients between serum and salivary anti-Dsg antibodies

Parameters		*r**	*P***
Serum anti-Dsg-1	Salivary anti-Dsg-1	0.897	0.000
Serum anti-Dsg-3	Salivary anti-Dsg-3	0.964	0.000

*Spearman correlation coefficient, ***P* value significant at <0.01.

Table 3: Correlations of serum and salivary anti-Dsg 1 and 3 with PDAI scores

Disease severity index	Serum anti-Dsg-1	Salivary anti-Dsg-1	Serum anti-Dsg-3	Salivary anti-Dsg-3
Total PDAI	0.931*	0.831*	0.948*	0.903*
OMPDAI	0.756*	0.725*	0.762*	0.745*

*Spearman's correlation coefficient, *P*=0.000 for all correlations; *P* value significant at <0.01. PDAI: Pemphigus disease area index, OMPDAI: Oral mucosal component of pemphigus disease area index

DISCUSSION

The present study aimed at evaluation of serum and salivary anti-Dsg1 and anti-Dsg3 IgG autoantibodies by ELISA and correlation of antibody levels with disease severity as measured by PDAI for each patient. In addition, we aimed to investigate the correlation of anti-Dsg1 and anti-Dsg3 autoantibodies in serum and saliva with the severity of oral mucosal involvement by incorporating the oral mucosal component of PDAI. Serum and salivary anti-Dsg1 and anti-Dsg3 ELISA were also performed on samples from 20 healthy control subjects.

First, in case of serum, the higher levels of serum anti-Dsg-3 IgG Abs as compared to mean serum anti-Dsg-1Abs obtained in the present study are in agreement with findings of Hallaji *et al.* who reported the mean serum anti-Dsg3 antibody titers of 179.35 ± 68.78 RU/mL with lower positive serum anti-Dsg1levels 78.61 ± 67.09 RU/mL. In their study also the control values were below the cut off.[10] Similarly, De *et al.* found serum anti-Dsg1 levels of 88.08 ± 77.75 RU/mL with higher mean serum anti-Dsg3 antibody titers of 134.52 ± 55.43 RU/mL.[15] The increased titers of serum Dsg-3 IgG autoantibodies as compared to serum anti-Dsg1 levels obtained in our study may be explained by the pivotal role of anti-Dsg3 in both the cutaneous and mucosal forms of PV as Dsg-3 has

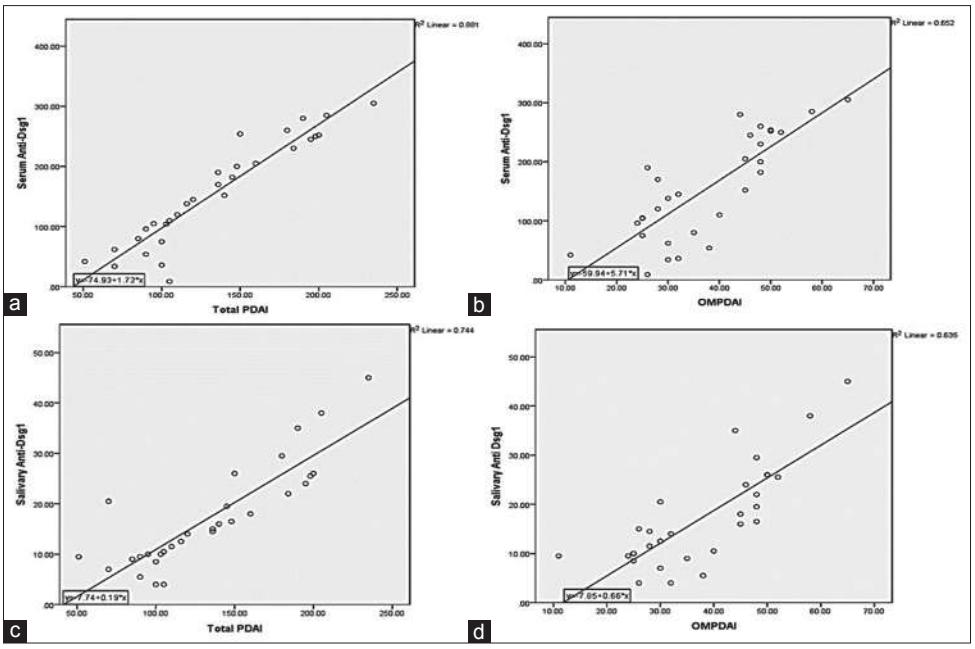

Figure 3: (a) The overall severity of disease (total pemphigus disease area index [PDAI]) positively correlated with serum anti-Dsg1 antibodies. (b) Positive correlation between serum anti-Dsg-1 values and oral mucosal disease severity (OMPDAI). (c) The overall severity of disease (total PDAI) positively correlated with salivary levels of anti-Dsg1 antibodies. (d) The oral mucosal disease severity (OMPDAI) positively correlated with salivary levels of anti-Dsg1 antibodies

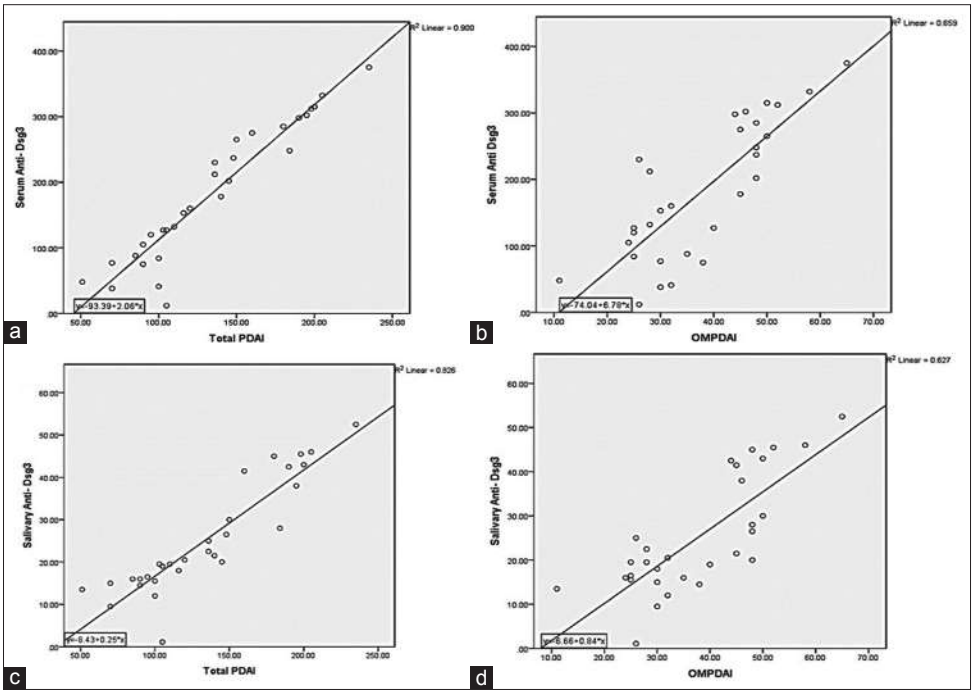

Figure 4: (a) The overall severity of disease (total pemphigus disease area index [PDAI]) positively correlated with serum anti-Dsg3 antibodies. (b) Positive correlation between serum anti-Dsg-3 values and oral mucosal disease severity (OMPDAI). (c) The overall severity of disease (total PDAI) positively correlated with salivary levels of anti-Dsg3 antibodies. (d) The oral mucosal disease severity (OMPDAI) positively correlated with salivary levels of anti-Dsg3 antibodies

widespread distribution in skin as well as mucosa while Dsg-1 is largely restricted to epidermis. As such, in our study all patients had extensive oral mucosal involvement besides cutaneous involvement.

However, even with lower titers the mean values of serum anti-Dsg1 Abs (154.46+/-88.91 RU/ml) obtained in our study as well as the sensitivity (93.33%) are much higher than most of the previous studies reported in the

literature.[10,16] This could be attributed to racial differences in serum levels of these antibodies as revealed by Harman *et al.* and Sharma *et al.*[9,17] The values obtained by us are higher than the serum anti-Dsg1 values of PV patients from northern Europe (46%) and Japan (53% and 55.6%) as reported by various studies.[9,18,19]

Anand *et al.* also conducted anti-Dsg1 and anti-Dsg3 ELISA on serum samples from 63 active PV patients and obtained sensitivity of about 74% in serum anti-Dsg-1. Similar to our results they found increased levels of both anti-Dsg3 and anti-Dsg1 in PV with the predominant distribution of anti-Dsg3 antibody. This could be explained by crosstalk between Dsg1 and Dsg 3 antigens and epitope spreading, as previously mentioned by Khandpur *et al.* and Chan *et al.*[17,19,20] Simply, Epitope spreading refers to a phenomenon in which that a primary autoimmune or inflammatory process may produce tissue damage in such a manner that certain protein components that are immunologically "hidden" from the immune system become "revealed" and subsequently evoke a secondary autoimmune response.[20] All our cases had extensive oral and cutaneous involvement and in almost all cases, the disease initiated with oral lesions subsequently spreading to skin. Several studies have emphasized that in mucocutaneous PV autoAbs recognize a secondary distinct epitope on Dsg-3 which cross-react with Dsg-1, inducing blister on mucosa and subsequently skin as explained by "epitope spreading".[20,21] However, the original response is directed against an epitope on Dsg-3 which is more accessible in mucosa.[21]

As regard saliva, in our study, we have obtained higher concentration of salivary anti-Dsg-3 antibodies as compared to anti-Dsg-1 antibodies in saliva. Studies in untreated patients have also reported higher IgG antibodies to Dsg3 in saliva in up to 70–94% of patients with PV.[8] In our results the serum IgG anti-Dsg-3 assay revealed 29 of 30 patients as positive and the salivary assay was positive for 27 of 30 patients. IgG antibodies present in saliva are derived mainly as a serum transudate from gingival crevicular fluid, mucosal inflammation, or through an ulcer along with the possibility of some direct passage of IgG across mucosa.[22] The difference may reflect healed mucosal lesions and reduced access to saliva of serum IgG. In addition, serum components, such as antibodies, could be transferred to saliva through capillary walls in the salivary glands.[10] Therefore, in patients with PV, serum anti-Dsg1 and anti-Dsg3 antibodies can be transmitted through the intercellular spaces between the cells to the lumen of salivary ducts through injured epithelial mucosa. Hence, its amounts mainly depend on the integrity of the epithelial barrier and tend to reflect serum levels.[23]

Importantly, there was statistically significant strong positive correlation between serum anti-Dsg titers with their salivary levels. Our results concur with the findings of previous studies. Hallaji *et al.* also obtained statistically significant correlation between serum and salivary anti-Dsg-1 and anti-Dsg-3 titers with $P < 0.001$ and 0.001, respectively.[10] Andrealis *et al.* found statistically significant correlation between serum anti-Dsg titers with their salivary levels ($P < 0.05$ for both associations).[16] In our study, the sensitivity of salivary Dsg3 ELISA was 86.66% and of Dsg1 ELISA was 83.33%. We found an association between salivary and serum values for both Dsg antibodies Therefore, salivary as well as serum samples, can be used for the assessment of anti-Dsg antibodies.

Another important aspect of the present study was correlation of Ab titers with disease severity. Our results indicate a significant positive correlation between serum and salivary levels of both Anti-Dsg 1 and 3 antibodies and overall disease severity (total PDAI). Further, we also attempted to explore whether or not there is correlation between salivary Desmogleins-1,3 and severity of oral mucosal involvement in PV patients by including oral mucosal component of PDAI for each patient (OMPDAI). Interestingly, levels of anti-Dsg 1 and 3 antibodies present in saliva positively correlated with severity of oral mucosal involvement (OMPDAI), with the strength of this correlation simulating the correlation of serum levels of these antibodies and severity of oral mucosal disease. On comparing salivary Dsg-1 and Dsg-3 Abs, the levels of salivary Dsg-3 autoantibodies better correlated with severity of oral mucosal disease much like its serum counterpart.

Mortazavi *et al.* also demonstrated that serum anti-Dsg 1 and anti-Dsg 3 values significantly correlated with total score of the disease. Further they showed that salivary anti-Dsg-1 and anti-Dsg-3 positively correlated with severity of mucosal disease. They concluded that salivary anti-Dsg 1, and anti-Dsg 3 ELISA, could be used as safe and noninvasive methods for the diagnosis of PV, when obtaining a blood sample is difficult (in certain circumstances, e.g., pediatric and senile patients).[11] Similarly Hallaji *et al.* concluded that serum Dsg-3 and salivary Dsg-1 antibody levels correlated with severity of mucosal lesions in PV patients.[10] However, another study was conducted to assess the relationship between salivary and serum Dsg1 and Dsg3 levels, and whether salivary Dsg1 and Dsg3 levels correlate with clinical disease severity of oral mucosal lesions in PV using objective component of the oral mucosal Autoimmune Bullous Skin Disorder Intensity Score (ABSIS).In this study no significant correlation of salivary titers with either mucosal or cutaneous disease severity was found.[15]

A recent systematic review and meta-analysis have shown that anti-Dsg ELISA is a valuable laboratory

diagnostic method for the initial diagnosis of autoimmune bullous diseases including PV and could be used in daily practice.[11,24]

ELISA is a quantitative method that has been extensively used to determine titers of Dsg1 and Dsg3 in sera of PV patients, and in this study these serum titers have been demonstrated to correlate with disease severity. However, there is little information on salivary Dsg1/Dsg3 levels using ELISA, or on the correlation between Dsg1/Dsg3 salivary levels and disease severity. In the present study, salivary anti-Dsg1 and anti-Dsg3 levels were found to correlate with their serum counterpart. In addition, our findings revealed a significant correlation of salivary Ab titers with total and oral mucosal disease severity closely simulating serum levels.

CONCLUSION

This study supports reports by previous literature indicating that saliva as well as serum could be used for detection of anti-Dsg1 and 3 antibodies by employing ELISA test. Serum anti-Dsg1 and anti-Dsg3 antibodies are reflective of disease severity in PV patients. Surprisingly, salivary anti-Dsg1 and anti-Dsg-3 antibodies significantly correlated with oral mucosal and overall disease severity and paralleled the correlations of same parameters with their corresponding serum counterparts. Therefore, Dsg ELISA using both serum and saliva is not only a sensitive tool for diagnosis of PV, it can also serve as a predictive means of its severity as well. Recently, there has been a surge in projects to develop miniaturized salivary diagnostic techniques which facilitate use of minute amounts of oral fluid to yield critical information regarding disease status. As such, easy and painless collection, possibility of repeated sampling along with ease of handling and storage makes saliva an attractive matrix for ELISA. According to the results of this study, the use of saliva Dsg ELISA for diagnosis of PV is comparable to its serum counterpart and may be a useful diagnostic screening tool for PV. However, further studies with larger sample sizes are recommended for demonstrating usefulness of saliva Dsg ELISA for diagnosis of PV.

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REFERENCES

1. Scully C, Challacombe SJ. Pemphigus vulgaris: Update on etiopathogenesis, oral manifestations, and management. Crit Rev Oral Biol Med 2002;13:397-408.
2. Cirillo N, Al-Jandan BA. Desmosomal adhesion and pemphigus vulgaris: The first half of the story. Cell Commun Adhes 2013;20:1-10.
3. Koopai M, Mortazavi H, Khatami A, Khodashenas Z. Salivary and serum anti-desmoglein 1 and 3 ELISA and indirect immunofluorescence in pemphigus vulgaris: Correlations with serum elisa, indirect immunofluorescence and disease severity. Acta Dermatovenerol Croat 2018;26:91-9.
4. Daneshpazhooh M, Chams-davatchi C, Khamesipour A, Mansoori P, Taheri A, Firooz A, *et al*. Desmoglein 1 and 3 enzyme-linked immunosorbent assay in Iranian patients with pemphigus vulgaris: Correlation with phenotype, severity, and disease activity. J Eur Acad Dermatol Venereol 2007;21:1319-24.
5. Amagai M, Tsunoda K, Zillikens D, Nagai T, Nishikawa T. The clinical phenotype of pemphigus is defined by the anti-desmoglein autoantibody profile. J Am Acad Dermatol 1999;40:167-70.
6. Ali S, Kelly C, Challacombe SJ, Donaldson AN, Bhogal BS, Setterfield JF. Serum and salivary IgG and IgA antibodies to desmoglein 3 in mucosal pemphigus vulgaris. Br Dermatol 2016;175:113-21.
7. Kuriachan D, Suresh R, Janardhanan M, Savithri V. Oral lesions: The clue to diagnosis of pemphigus vulgaris. Case Rep Dent 2015;2015:593940.
8. Beutner EH, Jordon RE. Demonstration of skin antibodies in sera of pemphigus vulgaris patients by indirect immunofluorescent staining. Proc Soc Exp Biol Med 1964;117:505-10.
9. Harman KE, Seed PT, Gratian MJ, Bhogal BS, Challacombe SJ, Black MM. The severity of cutaneous and oral pemphigus is related to desmoglein 1 and 3 antibody levels. Br J Dermatol 2001;144:775-80.
10. Hallaji Z, Mortazavi H, Lajevardi V, Tamizifar B, Amirzargar A, Daneshpazhooh M, *et al*. Serum and salivary desmoglein 1 and 3 enzyme-linked immunosorbent assay in pemphigus vulgaris: Correlation with phenotype and severity. J Eur Acad Dermatol Venereol 2010;24:275-80.
11. Mortazavi H, Khatami A, Seyedin Z, Farahani IV, Daneshpazhooh M. Salivary desmoglein enzyme-linked immunosorbent assay for diagnosis of pemphigus vulgaris: A noninvasive alternative test to serum assessment. Biomed Res Int 2015;2015:698310.
12. Amagai M, Komai A, Hashimoto T, Shirakata Y, Hashimoto K, Yamada T, *et al*. Usefulness of enzyme-linked immunosorbent assay using recombinant desmogleins 1 and 3 for serodiagnosis of pemphigus. Br J Dermatol 1999;140:351-7.
13. Barnadas MA, Rubiales MV, Gich I, Gelpí C. Usefulness of specific anti-desmoglein 1 and 3 enzyme-linked immunoassay and indirect immunofluorescence in the evaluation of pemphigus activity. Int J Dermatol 2015;54:1261-8.
14. Zagorodniuk I, Weltfriend S, Shtruminger L, Sprecher E, Kogan O, Pollack S, *et al*. A comparison of anti-desmoglein antibodies and indirect immunofluorescence in the serodiagnosis of pemphigus vulgaris. Int J Dermatol 2005;44:541-4.
15. De D, Khullar G, Handa S, Joshi N, Saikia B, Minz RW. Correlation between salivary and serum anti-desmoglein 1 and 3 antibody titres using ELISA and between anti-desmoglein levels and disease severity in pemphigus vulgaris. Clin Exp Dermatol 2017;42:648-50.
16. Andreadis D, Lorenzini G, Drakoulakos D, Belazi M, Mihailidou E, Velkos G, *et al*. Detection of pemphigus desmoglein 1 and desmoglein 3 autoantibodies and pemphigoid BP180 autoantibodies in saliva and comparison with serum values. Eur J Oral Sci 2006;114:374-80.
17. Anand V, Khandpur S, Sharma VK, Sharma A. Utility of desmoglein ELISA in the clinical correlation and disease monitoring of pemphigus vulgaris. J Eur Acad Dermatol Venereol 2012;26:1377-83.
18. Tallab T, Joharji H, Bahamdan K, Karkashan E, Mourad M, Ibrahim K. The incidence of pemphigus in the southern region of Saudi Arabia. Int J Dermatol 2001;40:570-2.
19. Khandpur S, Sharma V, Sharma A, Pathria G, Satyam A. Comparison of enzyme-linked immunosorbent assay test with immunoblot assay in the diagnosis of pemphigus in Indian patients. Indian J Dermatol Venereol Leprol 2010;76:27-32.
20. Chan LS, Vanderlugt CJ, Hashimoto T, Nishikawa T, Zone JJ, Black MM, *et al*. Epitope spreading: Lessons from autoimmune skin diseases. J Invest Dermatol 1998;110:103-9.
21. Ding X, Aoki V, Mascaro JM Jr., Lopez-Swiderski A, Diaz LA, Fairley JA. Mucosal and mucocutaneous (generalized) pemphigus vulgaris show distinct autoantibody profiles. J Invest Dermatol 1997;109:592-6.
22. Scully C, De Almeida OP, Porter SR, Gilkes JJ. Pemphigus vulgaris: The

manifestations and long-term management of 55 patients with oral lesions. Br J Dermatol 1999;140:84-9.
23. Gushi M, Yamamoto YI, Mine Y, Awazawa R, Nonaka K, Taira K, *et al*. Neonatal pemphigus vulgaris. J Dermatol 2008;35:529-35.
24. Tampoia M, Giavarina D, Di Giorgio C, Bizzaro N. Diagnostic accuracy of enzyme-linked immunosorbent assays (ELISA) to detect anti-skin autoantibodies in autoimmune blistering skin diseases: A systematic review and meta-analysis. Autoimmun Rev 2012;121:21-6.

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Original Article

Particle Size Matters: A Comparative Study of Transport of Encapsulated Iron through M Cells

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Abstract

Background and Objectives: Bioavailability of iron compounds is inversely related to their size. Decreasing particle size improves iron transport. However, bioavailability through the conventional DMT-1 pathway is hampered by mucosal block caused by hepcidin rise. This makes the microfold cells (M cells) in the intestine attractive targets for delivery of oral iron to systemic circulation. This study aimed to perform a comparative *in vitro* examination of different commercially available oral iron preparations and their transport across intestinal epithelial and M cells.

Method: An *in vitro* model of Caco-2 monoculture and Caco-2/Raji B co-culture was used to study transport across intestinal epithelial and M cells, respectively. The amount of elemental iron (Fe^{3+}) transported across was quantified using ICP-AES.

Results: Of all the iron salts that claim to transport through M cell mechanism, SunActive® Fe showed the highest transport (39.99%) whereas Lipofer® (0.48%) and Sideral® (10.26%) showed poor transport. SunActive® Fe showed the highest transport even through the intestinal endothelial Caco-2 cells and this transport is increased in presence of M cells.

Interpretation and Conclusion: This study paves the way to a greater understanding of therapeutic interventions for the treatment of iron deficiency anemia and identifies the most efficacious iron of those tested.

Key words: Bioavailability, Ferric pyrophosphate, Hepcidin, Iron Deficiency Anemia, M cells

INTRODUCTION

Iron is indispensable for the human body and a vital component of several bodily functions primarily, hemoglobin (Hb) synthesis, and transport of oxygen throughout the body. Proportionally, higher concentrations of iron are found in the basal ganglia of the human brain than in the liver. In breastfeeding infants, parts of the brain, particularly the microglia, continue to develop, and therefore iron is vital for developing cognitive functions at this stage of life.[1]

Anemia is a serious global public health problem that particularly affects young children and pregnant women. The World Health Organization (WHO) estimates that 42% of children <5 years of age and 40% of pregnant women worldwide are anemic.[2]

In spite of advances in healthcare, iron deficiency (ID) remains a foremost public health fear in both developed and developing countries, with adolescent women being mainly susceptible.[3] It affects all age groups including infants, adolescents, reproductive age group women, and elderly people. The prevalence rates for reproductive age group pregnant women and non-pregnant women are 29% and 38%, respectively; however, among different age groups, nearly 468 million women of reproductive age are commonly affected with anemia.[4]

Iron supplementation is the most commonly sought-after solution to prevent and treat iron deficiency and Iron Deficiency Anemia (IDA). Iron is supplemented by various methods such as oral, intravenous (IV) iron therapy, or blood transfusion. Red blood cell transfusion produces a rapid, albeit transient, rise in Hb, thus increasing oxygen-carrying capacity.[5] On the contrary, both IV and

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oral iron therapies restore iron levels and help maintain steady Hb levels. IV iron is administered directly into the bloodstream and therefore bypasses the gastrointestinal (GI) lumen. However, IV iron if not well tolerated can be toxic and may cause anaphylaxis and hypersensitivity reactions.[6] Moreover, IV iron is expensive, and costs over 60 times more than oral iron.[7] Oral iron is the most common treatment for ID and IDA due to its low cost, bioavailability, and effectiveness. While there are many different types of oral iron supplements available, the most commonly prescribed oral iron is ferrous sulfate ($FeSO_4$). However, an important clinical limitation of oral iron therapy is that it often causes significant gastrointestinal (GI) side effects such as constipation, abdominal pain, nausea, and bloating.[8]

The Challenges in Iron Absorption

Non-heme iron is majorly transported through the divalent metal transporter-1 (DMT-1).[9] DMT-1 is a protein expressed in the apical membrane of enterocytes.[10] Iron is taken up by the enterocyte through DMT-1 on the luminal membrane after reduction by a cytochrome Dyctb. Once inside the cell, iron can either be stored in ferritin or absorbed into the body circulation through ferroportin. Hephaestin, a ferroxidase converts the ferrous iron to ferric iron to be bound by transferrin.[11]

Iron linked to the mucous cells is carried into the intestinal lumen and thus lost, during the periodic desquamation which occurs within a mean period of 4–5 days. Apoferritin synthesis is inhibited in ID which further hinders iron absorption in the iron-deficient organism. This condition is known as the "mucosal block." Moreover, a number of other factors condition iron absorption, such as the chemical status of iron, presence of reducing agents, cofactors, dissociation from ligands to facilitate uptake by intestinal cells, and pathological processes associated with the GI tract, such as diarrhea, parasitic infestation or infections. With respect to the chemical status of iron, Fe^{2+} iron is readily absorbed by the body. However, excess free iron in the intestinal tract usually produces reactive oxygen species (ROS) triggering oxidative stress. In principle, the easier the dissociation of Fe^{2+} from oral iron supplements, the more serious is the intestinal inflammation.[12] For instance, despite being effective, Fe^{2+} iron has a tendency to trigger the Fenton reaction in the presence of hydrogen peroxide.[13] As a result, Fe^{2+} iron supplements have a high frequency of side effects in comparison to Fe^{3+} iron sources.[14] The reduction in iron concentration after the first pass through the liver greatly reduces its bioavailability.

Recurrent high doses of iron can potentially perturb the composition of the gut microbiome, enable pathogen abundance, and increase inflammation.[15] Hepcidin, a tight regulator of systemic iron levels in mammals, acts in concert with intracellular iron metabolism. High hepcidin levels block intestinal iron absorption and macrophage iron recycling, causing iron-restricted erythropoiesis and anemia. Low hepcidin levels favor bone marrow iron supply for Hb synthesis and red blood cell production.[16] Iron supplementation acutely increases the circulating plasma hepcidin level. Plasma hepcidin negatively correlates with iron bioavailability.[17] In a study by Moretti *et al.,* it was observed that hepcidin levels increased in iron-depleted young women with oral iron supplementation given daily or twice-daily, invariably decreases iron absorption from the subsequent doses.[18]

Other than the above-mentioned regulatory factors, intrinsic factors such as solubility, chemical nature, and particle size also affect iron absorption. The bioavailability of elemental iron powders has been shown to be inversely proportional to particle size. Decreasing particle size to the nanoscale could be a strategy to improve iron bioavailability.[19] Srinivasu *et. al.* showed that decreasing the particle size of FePP to nanoscale levels improved iron absorption leading to high bioavailability in iron-deficient rats. The relative bioavailability of FePP nanoparticles, calculated using Hb regeneration efficiency, was found to be 103.02% with respect to the reference salt, $FeSO_4$. This has been attributed to its reduced size which increased its solubility relative to its larger precursors.[20] It has been reported that $FeSO_4$ supplementation causes significant GI side effects in adults.[21] and may induce organoleptic changes when added to foods. On the contrary, $FePO_4$ is an iron compound that causes no adverse organoleptic changes in food matrices but is poorly absorbed (25%) relative to $FeSO_4$[22], limiting its nutritional value.

To bypass the rate-limited absorption via DMT-1 and to avoid the organoleptic changes caused by active iron, many have now turned to the Microfold cells (M cells) of the Peyer's patches (PPs) as an alternative mediator/target for efficient iron transport.

M Cells: Unconventional Cells with a Distinctive Role

The M cells of the PPs are so-called because they are covered with microfolds. M cells are advanced epithelial cells of the mucosa-associated lymphoid tissues (MALT). They are involved in the transfer of particles and microbes from the luminal side of the intestine to the lamina propria, where they are presented to the immune cells. They have been shown to provide a pathway for delivering orally administered vesicle-like particles to the systemic circulation through the lymphatic system.[23] Thus, they are widely researched as an alternative means of intestinal particle delivery to maximize bioavailability. It is generally agreed that transcytosis of particles increases

when the particle diameter decreases. Accordingly, M cells are capable of taking up particles from 50 nm to 10 μm, although particles in the 0.5–2 μm range are transcytosed most effectively.[24] In studies to determine the subsequent distribution of biodegradable microspheres, it was found that particles <5 μm can be transported through PPs to peripheral lymphoid organs, whereas particles >5 μm remain within PPs.[25] Within a range of 1–10 μm, particles in the 1–2 μm range appear to be preferentially taken up than the larger particles.[26] In a study by Desai *et al.*, the histological examination of the PPs and the non-patch samples showed a higher level of uptake for the 100 nm particles compared to larger size particles.[27] More studies on polystyrene latex revealed that the maximum number of absorbed nanoparticles occurred with particles ranging 50–100 nm in diameter, while particles above 1 μm were trapped in the PPs. Rieux *et al.* investigated the effect of physicochemical properties of nanoparticles on their transport across the human *in vitro* model of FAE. It was seen that the number of 0.2 μm transported nanoparticles was seven times higher ($P < 0.05$) than that of 0.5 μm nanoparticles.[28] Hence, it is generally accepted that particles below 1 μm are taken up by M cells and delivered in the basal medium, while particles larger than 5 μm are taken up by M cells but remain entrapped in PPs. Even if some controversy remains, the optimal size for a particle to be transcytosed by an M cell would be below 1 μm.[29]

Novel Encapsulated Ferric Pyrophosphates that Serve as Targets for M Cell Uptake

Lipid encapsulated FePP offers an easily scalable approach for the delivery of iron to human cells. Lipofer®, Sideral®, and SunActive® Fe are the three well-known examples of encapsulated FePPs used for transport through the M cells.

Lipofer® is ferric pyrophosphate encapsulated in liposomes[30] while Sideral® is a preparation of ferric pyrophosphate within a phospholipid and sucrester matrix.[31] SunActive® Fe is a micronized FePP coated with monoglycerides and diglycerides to minimize particle aggregation.

The purpose of the present study was to make a comparative analysis of M cell and intestinal absorption of the three widely used lipid encapsulated ferric pyrophosphates in an *in vitro* model of Caco-2 monoculture and Caco-2/Raji B coculture.

MATERIALS AND METHODS

An *in vitro* analysis to study the iron transport potential of three different commercial FePP through Caco-2 and Raji B cells using ICP-AES was performed at National Facility for Biopharmaceuticals, Mumbai. The three samples (raw material) tested were; SunActive® Fe, Lipofer®, and Sideral®.

Cell Culture

Caco-2 cells were purchased from National center for cell Sciences (NCCS), Pune, and cultured in growth media; Dulbecco's Modified Eagle Medium (DMEM; Thermo Fisher Scientific -11995065) under a humidified atmosphere (5% CO_2/95% air) at 37°C. The media were supplemented with 10% heat-inactivated FBS (Thermo Fisher Scientific –10437028), 100 units/ml of penicillin, and Primocin – (Biogene India – ant-pm-2).

Cell Culture for Intestinal Epithelial Monolayers

Caco-2 cells (monoculture), representing the intestinal epithelium monolayers of tight junctions, were prepared as follows; after coating Transwell inserts (CC INSERT MD6 3MY DIM 20/25 MM PC SI) with Matrigel matrix (Geltrex™ LDEV-Free Reduced Growth Factor Basement Membrane Matrix) for 1 h, supernatants were removed, and inserts washed with DMEM. Caco-2 cells (4.5×10^5 cells/well) were seeded on upper insert sides with 1.5 mL of growth media and cultured for 21 days. Media were replaced twice a week. After 21 days of incubation (37°C at 5% CO_2) of the cells, the medium was replaced from both apical as well as the basal layer of the cells and treated with the given samples (1500ppm of available Fe ion) on the apical side of the insert and incubated (37°C at 5% CO_2) for 6 h. The concentrations of transported Fe in basolateral solutions were determined by ICP-AES (Avio 500 ICP-OES, PerkinElmer**).**

Cell Culture for FAE Model

Caco-2 cells (4.5×10^5 cells/well) were grown on upper sides of the inserts in the same manner as described in the Caco-2 monoculture system and incubated (37°C at 5% CO_2) for 14 days. Raji B cells (4.5×10^5 cells/well) in DMEM were then added to basolateral insert compartments, and these co-cultures were maintained for 5 days. The apical side of the insert was replaced with fresh medium. Given samples (1500 ppm of available Fe ion) were added on the apical side of the insert and incubated for 6 h. Samples collected from the basolateral side of the insert, post-incubation, were centrifuged at 1500 rpm (REMI C20BL) for 10 min and the supernatant was used to determine the transported Fe by ICP-AES (Avio 500 ICP-OES, PerkinElmer). ICP-AES analysis was performed at Laxmi Analytical Laboratories, Mumbai.

RESULTS

Caco-2 cells transform into FAE-like cells in the presence of Raji B cells, and this model is an established *in vitro* model of intestinal enterocytes (Caco-2) and M cells (Raji B). To

determine the transport of micronized FePP through M cells, an *in vitro* analysis with three different commercially available FePPs was performed using Caco-2 and Raji B cells. The amount of iron transported was determined using ICP-AES.

In the monoculture model, the percentage of iron transported with SunActive® Fe was 27.51% (412.58 ppm of 1500 ppm loaded) followed by Lipofer® and Sideral® with 16.34% (245.03 ppm) and 15.14% (227.06 ppm) iron transport, respectively (Figure 1).

In the co-culture model, the percentage of iron transported from SunActive® Fe was significantly higher at 39.99% (599.84 ppm) as compared to Lipofer® and Sideral® with 0.48% (7.18 ppm) and 10.26% (153.91 ppm), respectively (Figure 2).

The percentage of iron transported SunActive® Fe was significantly higher in the co-culture system, indicating SunActive® Fe's selective uptake through the M cells.

Of note is that the percentage of iron transported through not only M cells but also through Caco-2 cells dropped in the case of Lipofer® and Sideral® in the co-culture.

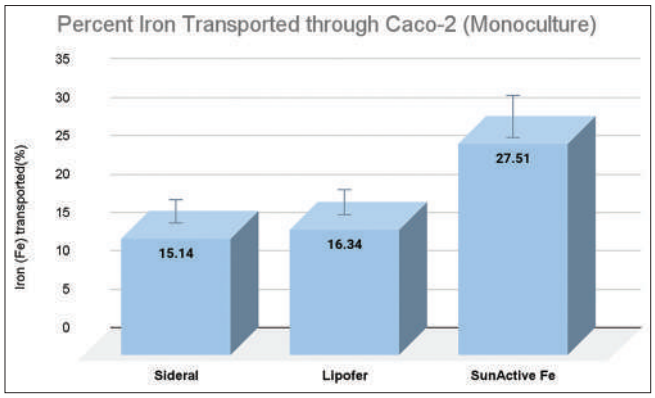

Figure 1: Comparison of percentage of iron transported in monoculture model

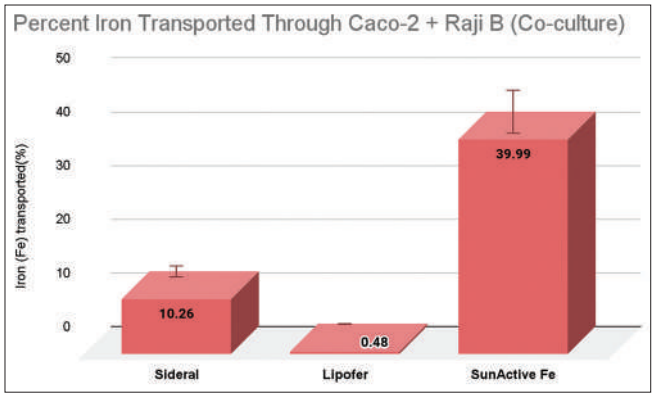

Figure 2: Comparison of percentage of iron transported in a co-culture model

DISCUSSION

Iron is an essential micronutrient and plays an important role in numerous physiological processes such as hematopoiesis, oxygen metabolism, energy production, brain health, and human well-being in general. IDA is still regarded as one of the major health concerns worldwide.

Conventional oral iron salts are poorly absorbed; consequently, the unabsorbed iron leads to several GI adverse effects and in turn reduces the patient's compliance. This undermines the long-term efficacy of oral iron supplements.

With an intent to improve iron bioavailability and effectively reduce the side effects of oral therapy, innovative approaches to novel dietary supplements such as microencapsulation, microsomes, liposomes, and sucrosomes have emerged and are being marketed.

The advantages of such alterations ensure the iron are protected through the digestive process, the release of unabsorbed iron is limited, resulting in enhanced bioavailability by utilizing contemporary intestinal routes of absorption which are not iron-dependent.

M cells serve a critical role in immune surveillance. Being morphologically distinct from the canonical enterocytes, M cells confer a new functional capability. Unique cellular mechanics of the M cells, capture the molecule at the apical membrane and transport them to the basolateral side from where the molecule is delivered to the dendritic cells.[32]

Due to its non-invasive nature, oral drug delivery is the route of choice, avoiding pain and discomfort, and enabling excellent patient compliance. However, some bioactive molecules remain poorly bioavailable if administered orally because of their lack of stability in the hostile GI environment, which results in degradation prior to absorption or a significantly reduced absorption.

The objective of this study was to determine the intestinal absorption mechanism of three encapsulated iron preparations SunActive® Fe, Lipofer® and Sideral®, employing the *in vitro* models of Caco-2 monolayer and human FAE, representing the intestinal endothelial and M cells in PPs, respectively.

This study was essential to independently understand the underlying mechanism and validate the claims about the three major FePP formulations being transported by M cells.

From the results, it can be seen that iron from SunActive® Fe was primarily transported by M cells, although transport

through Caco-2 monolayer was also seen. Our study was in accordance with the study carried out by Kim *et.al.*,[33] where the intestinal transport mechanism of SunActive® Fe was observed. The result demonstrated that SunActive® Fe was transported fundamentally through M cells. In the present study, percent of iron transported was greater from SunActive® Fe at 39.99 % when compared to the percent of iron transported by Lipofer® and Sideral®, which was 0.48% and 10.26%, respectively (Figures 1 and 2).

The results of the present study are in line with the previous findings on M cells that the particle size of the iron holds essence where M cells are utilized for transport of iron. The optimal size of a particle to be taken up by the M cells and trancytosed from the basolateral side is below 1 μm. In contrast, particles that are larger than 5 μm are absorbed by M cells but remain entrapped in the PPs for up to 35 days.[34] A reported particle size of 0.3–0.5 microns would be best suited for transport through M cells in line with our results.[33] Lipofer® with a particle size of 7 μm[35] and Sideral® with approximately 11–13 μm[36] may pass through M cells but will remain entrapped in the PPs and thus, may not display the desired results whereas the above will not be the case for SunActive® Fe with a particle size below 1 micron. This would be possible since the M cell would be able to endocytose the iron, but it would thereafter be trapped within the M cell or at the PPs due to its size. As per previously reported literature on particle size and M cell transport, as well as results from this study, only an iron with a particle size smaller than 1 μm would pass through the M cells.

Co-culture mimics the model of human intestinal FAE consisting of M cells. A reduction in iron transport observed with Lipofer® and Sideral® in the co-culture model could be attributed to the reduced surface area in the presence of Raji B cells along with Caco-2 cells as well as to the iron that gets trapped within the M cells with nowhere to go.

In the case of SunActive® Fe, a high oral absorption efficacy can be ascribed to its increased intestinal transport primarily through M cells and partly through Caco-2 monolayers, taking advantage of both the models studied.

The above data reiterates the importance of particle size in the absorption of molecules; in our case iron, through M cells, and validates SunActive® Fe as the most bioavailable iron compared to Lipofer® and Sideral®.

CONCLUSION

Recent advances in the use of M cells suggest their practical applications for optimal stimulation of immunological or physiological responses following oral administration. M cells are a unique mode of delivery for particulate drugs or bioactive, due to their ability to capture particles at the apical membrane and transport them to the basolateral end. Of the 3 encapsulated Ferric Pyrophosphate preparations, SunActive® Fe efficaciously makes use of this unique mechanism exhibited by M cells to bypass the conventional DMT-1 channels and directly reach the lymphatics, which may eventually result in superior absorption, bioavailability, and excellent patient compliance. Particle size plays a cardinal role in this unconventional delivery route; not all iron molecules absorbed through M cells can pass through PPs. As seen in the present study SunActive® Fe, the smallest available encapsulated FePP with a particle size below 0.5 microns, is predominantly transported through the M cells. This innovative approach can serve as a potent therapy for IDA, both prophylactically and therapeutically.

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ETHICS

Ethical permission not applicable as our study is *in vitro* and no human participants/animals were involved.

REFERENCES

1. Barragán-Ibañez G, Santoyo-Sánchez A, Ramos-Peñafiel CO. Iron deficiency anaemia. Rev Med Hosp Gen Méx 2016;79:88-97.
2. World Health Organization. Anaemia. Geneva: World Health Organization; 2022. Available from: https://www.who.int/health-topics/anaemia [Last accessed on 2022 May 09].
3. Dasa F, Abera T. Factors affecting iron absorption and mitigation mechanisms: A review. Int J Agric Sci Food Technol 2018;4:24-30.
4. Rahman KM, Ali KM, Vijayalakshmi S, Ramkumar S, Hashmi G. Prevalence of iron deficiency anaemia and its associated factors among reproductive age women in a rural area of Karaikal, Puducherry, India. J Clin Diagn Res 2019;13:LC6-10.
5. Muñoz M, Gómez-Ramírez S, Besser M, Pavía J, Gomollón F, Liumbruno GM, *et al*. Current misconceptions in diagnosis and management of iron deficiency. Blood Transfus 2017;15:422-37.
6. Macdougall IC, Vernon K. Complement activation-related pseudo-allergy: A fresh look at hypersensitivity reactions to intravenous Iron. Am J Nephrol 2017;45:60-2.
7. Lee TW, Kolber MR, Fedorak RN, van Zanten SV. Iron replacement therapy in inflammatory bowel disease patients with iron deficiency anemia: A systematic review and meta-analysis. J Crohns Colitis 2012;6:267-75.
8. Bloor SR, Schutte R, Hobson AR. Oral Iron supplementation-gastrointestinal side effects and the impact on the gut microbiota. Microbiol Res 2021;12:491-502.
9. Yanatori I, Kishi F. DMT1 and iron transport. Free Radic Biol Med 2019;133:55-63.
10. Przybyszewska J, Żekanowska E. The role of hepcidin, ferroportin, HCP1, and DMT1 protein in iron absorption in the human digestive tract. Prz Gastroenterol 2014;9:208-13.
11. Duck KA, Connor JR. Iron uptake and transport across physiological

barriers. Biometals 2016;29:573-91.
12. Qi X, Zhang Y, Guo H, Hai Y, Luo Y, Yue T. Mechanism and intervention measures of iron side effects on the intestine. Crit Rev Food Sci Nutr 2020;60:2113-25.
13. Winterbourn CC. Toxicity of iron and hydrogen peroxide: The Fenton reaction. Toxicol Lett 1995;82-83:969-74.
14. Pereira RC, Diniz AD, Ferreira LO. New findings on iron absorption conditioning factors. Rev Bras Saude Mater Infant 2004;4:241-8.
15. Jaeggi T, Kortman GA, Moretti D, Chassard C, Holding P, Dostal A, *et al*. Iron fortification adversely affects the gut microbiome, increases pathogen abundance and induces intestinal inflammation in Kenyan infants. Gut 2015;64:731-42.
16. Pagani A, Nai A, Silvestri L, Camaschella C. Hepcidin and anemia: A tight relationship. Front Physiol 2019;10:1294.
17. Roe MA, Collings R, Dainty JR, Swinkels DW, Fairweather-Tait SJ. Plasma hepcidin concentrations significantly predict interindividual variation in iron absorption in healthy men. Am J Clin Nutr 2009;89:1088-91.
18. Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, *et al*. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood 2015;126:1981-9.
19. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: A systematic review and meta-analysis. PLoS One 2015;10:e0117383.
20. Forbes AL, Arnaud MJ, Chichester CO, Cook JD, Harrison BN, Hurrell RF, *et al*. Comparison of *in vitro*, animal, and clinical determinations of iron bioavailability: International Nutritional Anemia Consultative Group Task Force report on iron bioavailability. Am J Clin Nutr 1989;49:225-38.
21. Kumari A, Chauhan AK. Iron nanoparticles as a promising compound for food fortification in iron deficiency anemia: A review. J Food Sci Technol 2022;59:3319-35.
22. Srinivasu BY, Mitra G, Muralidharan M, Srivastava D, Pinto J, Thankachan P, *et al*. Beneficiary effect of nanosizing ferric pyrophosphate as food fortificant in iron deficiency anemia: Evaluation of bioavailability, toxicity and plasma biomarker. RSC Adv 2015;5:61678-87.
23. Mabbott NA, Donaldson DS, Ohno H, Williams IR, Mahajan A. Microfold (M) cells: Important immunosurveillance posts in the intestinal epithelium. Mucosal Immunol 2013;6:666-77.
24. Rouch JD, Scott A, Lei NY, Solorzano-Vargas RS, Wang J, Hanson EM, *et al*. Development of functional microfold (M) Cells from intestinal stem cells in primary human enteroids. PLoS One 2016;11:e0148216.
25. Ermak TH, Dougherty EP, Bhagat HR, Kabok Z, Pappo J. Uptake and transport of copolymer biodegradable microspheres by rabbit Peyer's patch M cells. Cell Tissue Res 1995;279:433-6.
26. Ermak TH, Giannasca PJ. Microparticle targeting to M cells. Adv Drug Deliv Rev 1998;34:261-83.
27. Desai M, Labhasetwar V, Amidon GL, Levy RJ. Gastrointestinal uptake of biodegradable miroparticles: Effect of particle size. Pharm Res 1996;13:1838-45.
28. Rieux A, Ragnarsson EG, Gullberg E, Préat V, Schneider YJ, Artursson P. Transport of nanoparticles across an *in vitro* model of the human intestinal follicle associated epithelium. Eur J Pharm Sci 2005;25:455-65.
29. Des Rieux A, Fievez V, Garinot M, Schneider Y, Préat V. Nanoparticles as potential oral delivery systems of proteins and vaccines: A mechanistic approach. J Control Release 2006;116:1-27.
30. Navas-Carretero S, Pérez-Granados AM, Sarriá B, Vaquero M. Iron absorption from meat pate fortified with ferric pyrophosphate in iron-deficient women. Nutrition 2009;25:20-4.
31. Riccio E, Sabbatini M, Capuano I, Pellegrino AM, Petruzzelli LA, Pisani A. Oral sucrosomial® iron versus intravenous iron for recovering iron deficiency anaemia in ND-CKD patients: A cost-minimization analysis. BMC Nephrol 2020;21:51.
32. Dillon A, Lo DD. M cells: Intelligent engineering of mucosal immune surveillance. Front Immunol 2019;10:1499.
33. Kim HJ, Bae SH, Kim HJ, Kim KM, Song JH, Go MR, *et al*. Cytotoxicity, intestinal transport, and bioavailability of dispersible iron and zinc supplements. Front Microbiol 2017;8:749.
34. Diesner SC, Wang XY, Jensen-Jarolim E, Untersmayr E, Gabor F. Use of lectin-functionalized particles for oral immunotherapy. Ther Deliv 2012;3:277-90.
35. Navas-Carretero S, Pérez-Granados AM, Sarriá B, Schoppen S, Vaquero MP. Iron bioavailability from pate enriched with encapsulated ferric pyrophosphate or ferrous gluconate in rats. Food Sci Technol Int 2007;13:159-63.
36. Lacorte A, Tarantino G. Solid Composition Comprising Iron for Use in Iron Deficient Conditions. Available from: https://www.patentscope.wipo.int/search/en/detail.jsf?docId=WO2014009806 [Last accessed on 2021 Oct 11].

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Original Article

Preferred Topical Anesthesia in Reducing Injection Pain: A Randomized Clinical Trial

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Abstract

Aim: The purpose of this study was to compare the effectiveness of topical anesthetic agents, that is, 2% lidocaine gel, 20% benzocaine gel, and 5% EMLA cream in reducing needle insertion pain during extraction in children.

Materials and Methods: A total of 60 healthy children of both sexes from 5 to 9 years of age were selected and divided into three groups, that is, 2% lidocaine gel (Group 1), 20% benzocaine gel (Group 2), and 5% EMLA cream (Group 3). After application of topical anesthetic agent and needle insertion and before start of the extraction procedure, the objective and subjective pain responses of the children were evaluated using the visual analog scale, Wong-Bakers faces pain rating scale, and sound eye motor scales.

Results: No statistical significant difference was recorded between Group I (2% lidocaine gel) and Group II (20% benzocaine gel) in reducing pain intensity during needle insertion. Topical anesthetic in Group III, that is, 5% EMLA cream showed statistically significant better results in effectively reducing pain when compared to other two topical anesthetics used in the study.

Conclusion: The present study concluded that 2% lignocaine is equally effective with 20% benzocaine gel in reducing the pain intensity of needle insertion. Topical anesthetic based on a combination of 2.5% lidocaine and 2.5% prilocaine (EMLA) reduced pain significantly better when compared with 2% lignocaine and 20% benzocaine.

Key words: Benzocaine, EMLA, Lidocaine, Pain perception, Sound eye motor scale, Topical anesthesia, Wong-baker faces pain rating scale

INTRODUCTION

Dental treatment for children has always been difficult due to the emotional attribute of dental anxiety.[1] Reduced pain during dental procedures can serve to strengthen the bond between the child patient and the dentist, building trust, and promoting positive behavioral attitude.[2]

Topical anesthetics have the ability to penetrate the oral mucosa and induce anesthesia.[1] Lignocaine and benzocaine are the most commonly used topical anesthetic agents. EMLA, a eutectic combination of local anesthetic drugs, has proven to be effective in the relief of pain associated with various minor dental interventions in adults and children.

Hence, the present study compared the effectiveness of three different topical anesthetics, that is, lidocaine gel, benzocaine gel, and EMLA cream in reducing needle insertion pain during extraction in children.

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MATERIALS AND METHODS

This *in vivo* study was conducted at the Department of Pediatric and Preventive Dentistry, K. D. Dental College and Hospital, Mathura, on a total of 60 healthy children of both sexes from 5 to 9 years of age using the inclusion and exclusion criteria. Children with a non-contributory medical history, being mentally able to complete the facial pain rating scale (FPS) [Figure 1], and visual analog scale (VAS) [Figure 2] and both maxillary and mandibular primary anterior teeth with need for extraction were included in

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the study. Children with any medical problems, behavioral problems, or with special health-care needs were excluded from the study.

The research protocol was reviewed by the Ethical Committee before conducting the study. Nature of the study was explained to the parents or guardians and written consent was taken before starting of the study. Trial design was parallel with allocation ratio of 1:1. The selected subjects were assigned into three groups having equal number of samples through chit system.

Pre-operative examination was done to assure proper case selection. The patient is asked to pick up a chit for the corresponding group of topical anesthetic to be applied [Figures 3 and 4].

- Group 1: 2% lidocaine gel
- Group 2: 20% benzocaine gel
- Group 3: 5% EMLA cream.

The area of application of topical anesthetic was air dried with a three-way air syringe. Dry field was obtained by use of cotton roll isolation before topical anesthetic application. Slow speed suction was used to for better isolation. Respective topical anesthetic agent was applied to the site by cotton applicator tip for 2-min [Figure 5] and after which needle insertion was done following injecting of local anesthetic agent [Figure 6]. The patient was, then, asked to complete the Wong-Bakers faces pain rating scale (WBFPRS) for that side of mouth by circling the corresponding FPS pictogram and mark a vertical line along the 100 mm VAS [Figure 7] and an examiner recorded the child's response of pain or discomfort according to the sound eye motor (SEM) scale components [Figures 8 and 9]. No instructions were given regarding the procedure or the use of VAS and WBFPRS to the child before the study to eliminate bias due to anticipated pain. The pain score for each of the test sites was recorded.

The recorded data were analyzed using the Statistical Package for the Social Sciences version 22.0. The results were statistically analyzed using one-way ANOVA, Student t-test, and Chi-square test. The level of statistical significance was set at 95% ($P = 0.05$) and $P < 0.05$ was considered statistically significant.

Table 1: Comparison of pain perception of patients using visual analog scale between groups

Group	*N*	Mean	SD	F-value	*P*-value
Lidocaine	20	2.60	0.59	21.38	0.001*
Benzocaine	20	2.85	0.82		
EMLA	20	1.45	0.63		

*Significant

Table 2: Comparison of pain perception of patients using facial pain rating scale (FPS) between groups

Group	*n*	Mean	SD	F-value	*P*-value
Lidocaine	20	2.40	0.73	11.68	0.001*
Benzocaine	20	2.90	0.64		
EMLA	20	1.90	0.85		

*Significant

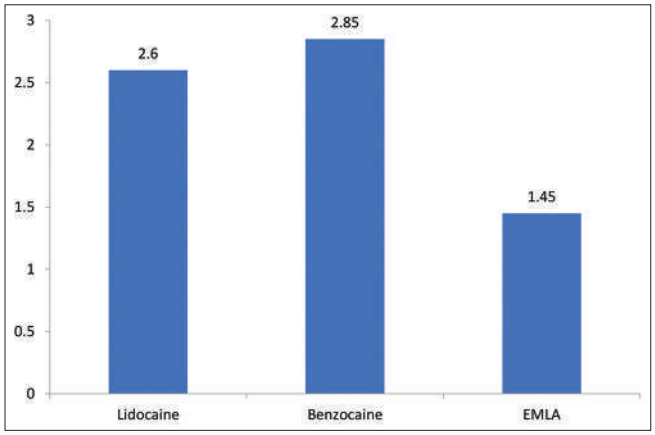
RESULTS

Assessing the pain of the patients using VAS showed that the mean VAS score in lidocaine group was 2.60 ± 0.59 while in benzocaine group was 2.85 ± 0.82 and in EMLA group was 1.45 ± 0.63. One-way ANOVA was used to compare the different groups and showed significant difference between the groups with $P = 0.001$. Therefore, the pain recorded according to VAS scale showed Group I (lidocaine) and Group II (benzocaine) to be similarly effective in reducing pain during needle insertion but less than Group III (EMLA) [Table 1 and Graph 1].

Assessing the pain of the patients using Wong-Baker's FPS with mean FPS score 2.40 ± 0.73, 2.90 ± 0.64, and 1.90 ± 0.85, respectively, for Group 1, Group II, and Group III. One-way ANOVA was used to compare different groups showed significant difference between the groups with F-value 11.68 and $P = 0.001$. Therefore, the pain recorded for all the three groups according to FPS scale showed

Figure 1: Wrong-baker pain scale

Group I (lidocaine) and Group II (benzocaine) to be similarly effective in reducing pain during needle insertion but comparatively less than Group III (EMLA) [Table 2 and Graph 2].



Graph 1: Comparison of pain perception of patients using visual analog scale between groups

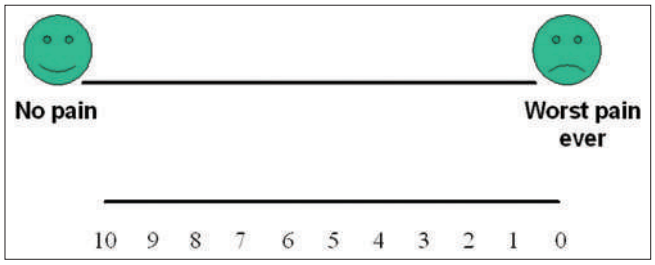


Figure 2: Visual analog scale

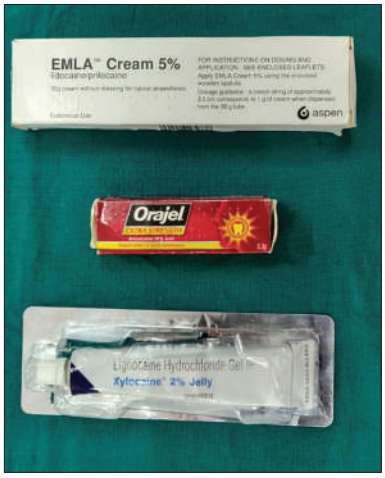


Figure 3: Material used

The SEM scale was used to compare the pain between groups. In Group I (lidocaine), seven patients were comfortable, 12 patients had mild discomfort, and one patient moderately painful. In Group II (Benzocaine), five patients were comfortable, 13 patients had mild discomfort, and two patients moderately painful. In Group III (EMLA), 14 patients were comfortable, six patients had mild discomfort. Chi-square test was used to compare between the groups showed significant difference between groups with Chi-Square value 9.92 and $P = 0.042$ [Table 3 and Graph 3].

In SEM scale, the pain in groups was further compared using Chi-square test showed following result. Therefore, the pain recorded for the three groups according to SEM scale showed Group I (lidocaine) and Group II (benzocaine) to be similarly effective in reducing pain during needle insertion but comparatively much less than Group III (EMLA) [Table 4].

DISCUSSION

Fear and anxiety are the most prevalent problems in pediatric dentistry. Needle phobias most precisely, fear of pain due to needle prick is the most frequently encountered discomfort in a child, which compromises their dental health.[3] Local anesthesia is an imperative part of dentistry. The effective treatment of pediatric children is by pacifying their fear and distress during dental treatment is aided by the use of a profound local anesthetic.[4] Local anesthesia is a combination of two Greek words "an" (without) and "esthesis" (sensation). The first local anesthetic was a topical anesthetic, that is, cocaine and was discovered in 1860 by Albert Niemann.[5]

Topical anesthetics exhibit pharmacological as well as psychological benefits.[6] Creams, ointment, gel, eutectic mixtures, patches, cellulose discs, and sprays have been used as different modes of topical anesthesia.[7] In the present study, it was decided to opt for topical anesthetic gels and creams which were used regularly in pediatric dental practice as it reduces or eliminates pain during the injection procedure having an advantage of locally targeting the drug, better control over systemic drug absorption, offering a greater bioavailability, and reduction in dosage. The use of

Table 3: Comparison of pain perception of patients between groups using SEM scale

Score	Group Lidocaine	Group Benzocaine	Group EMLA	χ^2 value	*P*-value
1.00 (comfort)	7	5	14	9.92	0.042*
2.00 (mild discomfort)	12	13	6		
3.00 (moderately painful)	1	2	0		
4.00 (painful)	0	0	0		

*Significant

Figure 4: Lottery system

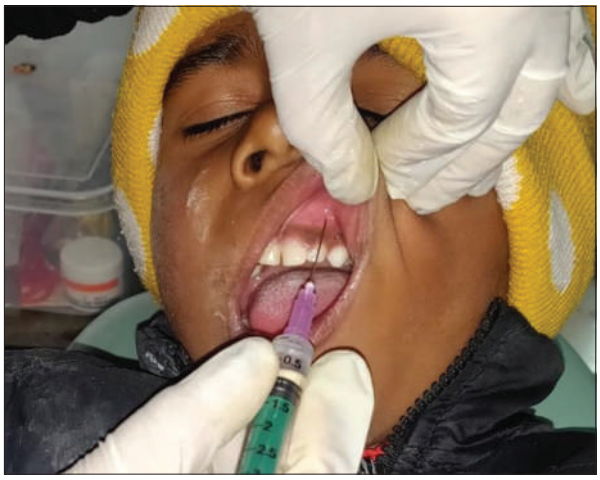


Figure 6: Needle penetration

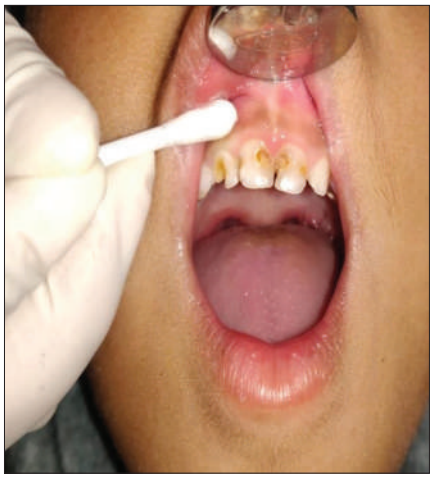


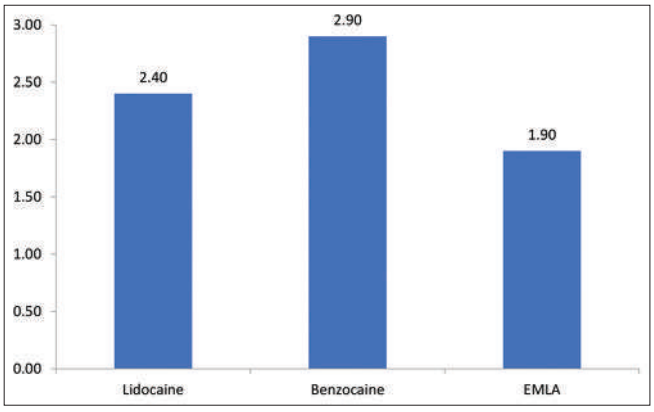
Figure 5: Topical anesthetic

Figure 7: Self assessment (VAS and FPS)

topical anesthetic before the injection of a local anesthetic to reduce discomfort associated with needle penetration has been recommended by the American Academy of Pediatric Dentistry.

The objective of the current trial was to assess the efficacy of three topical anesthetic agents (2% lidocaine, 20% benzocaine, and 5% EMLA cream) on pain perception in pediatric patients requiring anterior buccal infiltration for extraction procedures which were recruited.

Benzocaine, widely used ester type anesthetic, has rapid onset of action (30 s), acceptable pleasant taste, effectiveness, and lack of systemic absorption.[8] Lignocaine is most widely used local anesthetic agent and has quicker onset of action (3–5 min) and peak effect being achieved by 8–11 min and besides having excellent anesthetic efficacy, it has limited allergenicity.[9] Another topical anesthetic agent introduced in the 1980's was EMLA. The use of EMLA has been explored in various clinical procedures, such as the placement of rubber dam clamps, extraction of mobile



Graph 2: Comparison of pain perception of patients using facial pain rating scale between groups

primary teeth, soft-tissue biopsies, and removal of arch bars after intermaxillary fixation.[10-19] The superior surface anesthetic property of EMLA could be attributed to its high pH (pH 9.6). EMLA had less bitter taste and lacks odor. Its ability to be applied and get absorbed by the mucosa is easy and has a much longer duration of action (60 min).[20]

Observations	1 Comfort	2 Mild discomfort	3 Moderately Painful	4 Painful
Sounds	No sounds indicating pain	Non-specific sounds; possible pain indications	Specific verbal complaints "OW" raises voice	Verbal complaint indicates intense pain, e.g. Scream, sobbing.
Eyes	No eye signs of discomfort	Eyes wide, show of concern, no tears	Watery eyes, eyes flinching	Crying, tears running down face
Motor	Hands relaxed no apparent body tenseness	Hands show some distress or tension; grasps chair due to discomfort, muscular tension	Random movement of arms or body without aggressive intention of physical contact, grimace, twitch	Movement of hands to make aggressive contact, e.g. Punching, pulling head away

Figure 8: Sound eye motor scale

Figure 9: Assessment using SEM scale

Table 4: Comparison of SEM scale scores between groups

Comparison group	χ^2 value	*P*-value
Group I versus Group II	0.70	0.71
Group I versus Group III	6.33	0.044*
Group II versus Group III	8.84	0.012*

*Significant

In the present study, 5% EMLA cream was found to be superior to 20% benzocaine gel and 2% lignocaine gel with regard to pain reduction which was in accordance with the study by Al-Melh and Andersson[13] Holst and Evers and Vickers and Punnia-Moorthy[11] reported superiority of EMLA 5% over xylocaine and NUM. Tulga and Mutul[21] reported that vision gel (benzocaine 20%) was superior in performance compared to EMLA 5%. However, Meechan and Donaldson stated that EMLA and lignocaine 5% were equally effective.

A variety of factors have been reported to influence the effectiveness of topical anesthetics.

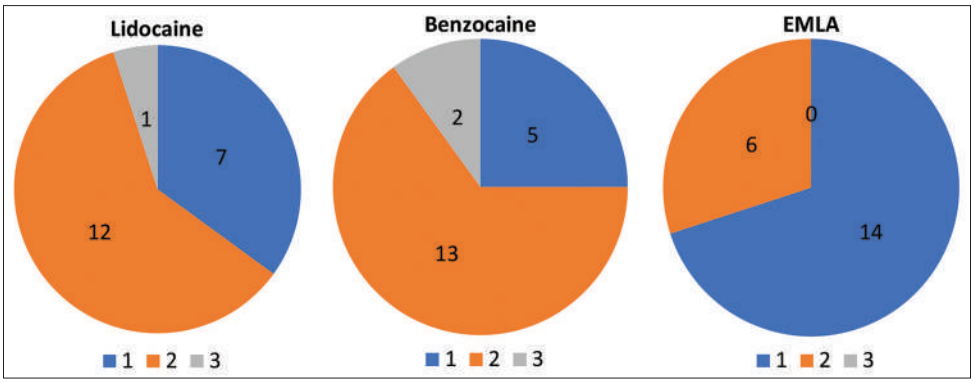
Several studies showed that topical anesthetic effectiveness was found to be related to the location of the injection. In the present study, we chose to test the effects of the topical anesthetics in the maxillary and mandibular anterior buccal mucosa which was in accordance with the study by Nusstein and Beck[22] In general, topical anesthetics seem to work if applied to either the maxillary or mandibular buccal fold as shown in several randomized clinical trials.[11,23-25]

The duration of application is another factor. Increasing the duration of exposure to the topical anesthetic has been related to increased effectiveness. Hutchins *et al.*[26] also reported success in the maxillary mucobuccal fold with a 1-min application of 20% benzocaine. Holst and Evers,[24] Bhalla *et al.*,[27] and Vongsavan and Vongsavan[28] reported success with a 2-min application. In the present study, a topical application for a minimum of 2 min was observed to be essential for obtaining a reasonably good surface anesthesia for EMLA cream which was in accordance with the study by Vickers and Punnia-Moorthy.[11]

Care was taken in our study to standardize the procedure of injection, such as wiping the mucosa dry before topical application to maximize the effect of the topical anesthetic, application time of 2-min, use of smaller gauge needle, slow rate of injection, and verbal suggestion. This was in accordance with the study by Sharma *et al.*[29]

Quantifying pain remains one of the most challenging tasks for researchers, especially when working with children. Due to the developmental, cognitive, and emotional differences between adults and children, assessment of pain is even more difficult in children. In general, patient's self-report is considered to be a reliable and effective way of measuring pain.[29] It is clinically important to note that uncooperative children can give inaccurate pain assessment, and hence, the children selected for this study were cooperative. Two different types of scales (subjective and objective) were used to assess pain. The WBFPRS, VAS, and SEM pain scales were included in the present study.

In our present study, statistical data show that there was a significant difference in pain perception among the three groups concerning subjective and objective/behavioral responses. Pain perception in the EMLA (Group III) was



Graph 3: Comparison of pain perception of patients between groups using SEM scale

significantly lower compared to that in the benzocaine (Group II) and lidocaine (Group I) groups whereas, no significant difference in pain perception was observed between the benzocaine (Group B) and lidocaine (Group A) gel groups. This finding is contrary to the study performed by Primosch and Rolland-Asensi[12] and Tulga and Mutul[21] where they found benzocaine 20% gel to be better than or similarly effective as EMLA 5% cream. Contrary to this, a study by Nayak and Sudha[30] concluded that 5% of EMLA cream provided superior pain reduction which was in accordance with our study. Similarly, there are studies supporting the fact that EMLA is effective in reducing pain similar to our study.[12,13,20,31-33] A study by Garg *et al.* concluded that the effectiveness of both 2% lidocaine and 20% benzocaine gels was similar as in our study.[34]

The findings of the current randomized clinical trial establish the notion that the use of 5% EMLA cream as a topical anesthetic agent before needle injection for dental extractions or other dental procedures increases the tolerance to injection, while a local anesthetic is being administered and aids in the management of the pediatric patient during such dental procedures. The superiority of EMLA cream in the present study could be attributed to its high pH of 9.6. This is in accordance with Setnikar *et al.* who stated that increasing the pH increases the potency of the topical anesthetic agent. Furthermore, a combination of two drugs in a single agent could have contributed to the increased efficiency.

Keeping the limitations in mind, a larger sample size in future studies would minimize the effect of these variables and provide a more conclusive result.

CONCLUSION

Fear is the most difficult aspect of patient management and also is a barrier to achieving good dental care. The prevalence of dental anxiety and fear is more in children when compared with adults and can affect the quality of care rendered to children by pediatric dentists. Topical or surface anesthesia is an important prerequisite for many pediatric dental procedures. The pediatric dentist should be well versed with type, duration, and the quantity of topical anesthesia to be administered in achieving maximum efficiency, without the risk of toxicity. 5% EMLA cream was comparatively better than 2% lignocaine gel and 20% benzocaine gel with regard to pain reduction during the administration of local anesthetic injection in children before extraction procedures and can thus be used effectively as an alternative in daily clinical practice.

REFERENCES

1. Walimbe H, Muchandi S, Bijle MN, Bendgude V, Deshpande R, Dolas A, *et al*. Comparative evaluation of the efficacy of topical anesthetics in reducing pain during administration of injectable local anesthesia in children. World J Dent 2014;5:129-33.
2. Mohite VA, Baliga S, Thosar N, Rathi N, Khobragade P, Srivastava R. Comparative evaluation of a novel herbal anesthetic gel and 2% lignocaine gel as an intraoral topical anesthetic agent in children: Bilateral split-mouth, single-blind, crossover *in vivo* study. J Indian Soc Pedod Prev Dent 2020;38:177-83.
3. Havale R, Rao DG, Shrutha SP, Tuppadmath KM, Tharay N, Mathew I, *et al*. Comparative evaluation of pain perception following topical application of clove oil, betel leaf extract, lignocaine gel, and ice prior to intraoral injection in children aged 6-10 years: A randomized control study. J Dent Anesth Pain Med 2021;21:329-36.
4. Lakshmanan L, Ravindran V. Efficacy of cryotherapy application on the pain perception during intraoral injection: A randomized controlled trial. Int J Clin Pediatr Dent 2021;14:616-20.
5. Vafaei A, Rahbar M, Dadkhah R, Ranjkesh B, Erfanparast L. Children's pain perception and behavioral feedback during local anesthetic injection with four injection site preparation methods. Maedica (Bucur) 2019;14:343-9.
6. Deepika A, Rao CR, Vinay C, Uloopi KS, Rao VV. Effectiveness of two flavored topical anesthetic agents in reducing injection pain in children: A comparative study. J Clin Pediatr Dent 2012;37:15-8.
7. Bhushan NV, Nayak RN. A comparison of the efficacy of topical application of lignocaine hydrochloride 5% gel and bupivacaine hydrochloride 5% gel for extraction of teeth. J Maxillofac Oral Surg 2010;9:119-26.
8. Leyda AM, Llena C. Comparation of the eutectic mixture of lidocaine/prilocain versus benzocaine gel in children. Open J Stomatol 2011;1:84-91.
9. Hawkins JM, Moore PA. Local anesthesia: Advances in agents and techniques. Dent Clin North Am 2002;46:719-32.
10. Haasio J, Jokinen T, Numminen M, Rosenberg PH. Topical anaesthesia of gingival mucosa by 5% eutectic mixture of lignocaine and prilocaine or by

10% lignocaine spray. Br J Oral Maxillofac Surg 1990;28:99-101.
11. Vickers ER, Punnia-Moorthy A. A clinical evaluation of three topical anaesthetic agents. Aust Dent J 1992;37:267-70.
12. Primosch RE, Rolland-Asensi G. Comparison of topical EMLA 5% oral adhesive to benzocaine 20% on the pain experienced during palatal anesthetic infiltration in children. Pediatr Dent 2001;23:11-4.
13. Al-Melh MA, Andersson L. Comparison of topical anesthetics (EMLA/ Oraqix vs. benzocaine) on pain experienced during palatal needle injection. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:e16-20.
14. Meechan JG. Effective topical anesthetic agents and techniques. Dent Clin N Am 2002;46:759-66.
15. Donaldson D, Gelskey SC, Landry RG, Matthews DC, Sandhu HS. A placebo-controlled multi-centred evaluation of an anaesthetic gel (Oraqix) for periodontal therapy. J Clin Periodontal 2003;30:171-5.
16. Herdevall BM, Klinge B, Persson L, Huledal G, Abdel-Rehim M. Plasma levels of lidocaine, o-toluidine, and prolicaine after application of 8.5 g oraqix in patients with generalized periodontitis: Effect on blood methemoglobin and tolerability. Acta Odontol Scand 2003;61:230-4.
17. Vickers ER, Marzbhani N, Gerziftoil TM, McLean C, Punnia-Moorthy A. Pharmacokinetics of EMLA cream 5% applications to oral mucosa. Anesth Prog 1997;44:32-7.
18. Meechan JG. The use of EMLA for an intraoral soft-tissue biopsy in a needle phobic: A case report. Anesth Prog 2001;48:32-4.
19. Lim S, Julliard K. Evaluating the efficacy of EMLA topical anesthetic in sealant placement with rubber dam. Pediatr Dent 2004;26:497-500.
20. Dhawan P, Dhawan G. Topical anaesthetic: How effective are they. Int J Dent Clin 2011;3:11-3.
21. Tulga F, Mutul Z. Four types of topical anaesthetic agents: Evaluation of clinical effectiveness. J Clin Pediatr Dent 1999;23:217-20.
22. Nusstein JM, Beck M. Effectiveness of 20% benzocaine as a topical anesthetic for intraoral injections. Anesth Prog 2003;50:159-63.
23. Rosivack RG, Koenigsberg SR, Maxwell KC. An analysis of the effectiveness of two topical anesthetics. Anesth Prog 1990;37:290-2.
24. Gill CJ, Orr DL 2nd. A double-blind crossover comparison of topical anesthetics. J Am Dent Assoc 1979;98:213-4.
25. Holst A, Evers H. Experimental studies of new topical anesthetics on the oral mucosa. Swed Dent J 1985;9:185-91.
26. Wu SJ, Julliard K. Children's preference of benzocaine gel versus the lidocaine patch. Pediatr Dent 2003;25:401-5.
27. Bhalla J, Meechan JG, Lawrence HP, Grad HA, Haas DA. Effect of time on clinical efficacy of topical anesthesia. Anesth Prog 2009;56:36-41.
28. Vongsavan K, Vongsavan N. Comparison of topical anesthetic gel and TENS in reducing pain. J Dent Res 1996;75:248.
29. Sharma A, Suprabha BS, Shenoy R, Rao A. Efficacy of lignocaine in gel and spray form during buccal infiltration anesthesia in children: A randomized clinical trial. J Contemp Dent Pract 2014;15:750-4.
30. Nayak R, Sudha P. Evaluation of three topical anaesthetic agents against pain: A clinical study. Indian J Dent Res 2006;17:155-60.
31. Agarwal N, Dhawan J, Kumar D, Anand A, Tangri K. Effectiveness of two topical anesthetic agentsused along with audio visual aidsin pediatric dental patients. J Clin Diagn Res 2017;11:ZC80-3.
32. Dabagh RA, Bianchi A, Brown Z, Chung AM, Kim HY, Ryan T. How effective are topical anesthecs for additional apin reliefin children during dental treatmentand post operatively. University of Toronto, Faculty of Dentistry 2012;1-13.
33. Roghani S, Duperon DF, Barcohana N. Evaluating the efficacy of commonly used topical anesthetics. Pediatr Dent 1999;21:197-200.
34. Garg A, Garg N, Kaur D, Sharma S, Tahun IA, Kumar R. Evaluation of efficacy of 2% lidocaine gel and 20% benzocaine gel for topical anesthesia. Endodontology 2016;28:38-41.

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Original Article

Disease Response Rate to Rituximab-cyclophosphamide, Hydroxydaunorubicin, Oncovin, and Prednisolone Regimen for Follicular Lymphoma

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Abstract

Background and Objective: Many clinical trials conducted in the western population have shown that the addition of rituximab to cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisolone (CHOP) regimen provided a higher response rate and excellent early survival in follicular lymphoma. This study aimed to assess the disease response rate to Rituximab-CHOP regimen for follicular lymphoma in Indian population.

Methods: From January 2015 to January 2016, 32 patients with histopathologically proven *de novo* follicular lymphoma who were prescribed Rituximab-CHOP regimen once every 21 days for 6–8 cycles were included in the study. Disease response rate at 1 month after completion of chemotherapy regimen was studied.

Results and Discussion: Age range of the study population was from 37 to 83 years. About 78.125% patients were male. Most of the patients belonged to Ann Arbor Stage III/IV. About 90.625% patients showed positive response to treatment at the end of 1 month after completion of chemotherapy schedule.

Conclusion: Response rate to treatment with Rituximab-CHOP regimen at the end of 1 month after completion of chemotherapy schedule was 90.625.

Key words: Disease response rate, Follicular lymphoma, Rituximab, Rituximab-CHOP regimen

INTRODUCTION

Lymphomas make up 3–4% of all cancers, making them the seventh-most common form.[1,2] Non-Hodgkin's lymphomas (NHL) are neoplastic transformations of mature B, T, and natural killer cells. NHL infiltrates lymphohematopoietic tissues and is among the most sensitive malignancies to radiation and cytotoxic therapy.

Rituximab-cyclophosphamide, Hydroxydaunorubicin, Oncovin, and Prednisolone (CHOP) regimen is a chemotherapy regimen for follicular lymphoma. This study assesses the disease response rate to this regimen for follicular lymphoma in Indian population.

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Aim

This study was a prospective single-arm observational study on disease response rate to Rituximab-CHOP regimen for follicular lymphoma given in a tertiary care setting.

Objective

The objective of this study was to study the disease response rate to Rituximab-CHOP regimen for follicular lymphoma.

Study Design and Setting

A prospective single-arm observational study in the Department of Radiotherapy, Medical College, Thiruvananthapuram, with 32 consecutive patients diagnosed by histopathology to have de novo follicular lymphoma and planned to be started on Rituximab-

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CHOP regimen, from the date of ethical clearance (January 09, 2015), for a period of 1 year (IEC No: 01/33/2015/MCT).

MATERIALS AND METHODS

Selection and Description of Participants

Study Design

This study was prospective single-arm observational study.

Study Setting

This study was Department of Radiotherapy, Government Medical College, Thiruvananthapuram.

Study Period

This study was January 2015 to January 2016.

Study Population

This study was patients with histopathologically proven *de novo* follicular lymphoma who are prescribed R-CHOP regimen.

Sample Size

The sample size was 32.

Sample size calculation

The response rate to Rituximab-CHOP regimen among patients with follicular lymphoma is 75%.[3]

This finding is used to calculate the sample size of the present study.

Sample size, $n = (t\ \alpha/z)^2\ pq/d^2$ Response rate, $P = 75\%$ Precision, d = 20% of p Significance level = 5% $n = 32$.

Sampling technique

Consecutive patients attending radiotherapy OPD diagnosed to have follicular lymphoma and started on Rituximab-CHOP regimen.

Inclusion Criteria

The following criteria were included in the study:

- Patients with histopathologically proven *de novo* follicular lymphoma started on Rituximab-CHOP regimen who have not received any other disease specific treatment.
- Patients who give informed consent.
- Age above 18 years.
- Both males and females.

Exclusion Criteria

The following criteria were excluded from the study:

- Pregnancy and breastfeeding patients.

Technical Information

Study tools

1. Chemotherapy Protocol
2. Semi-structured questionnaire
3. Revised response criteria for malignant lymphoma
4. Informed consent form-English and Malayalam
5. Follicular lymphoma international prognostic index (FLIPI).

Study procedure

Rituximab-CHOP regimen is given in the Department of Radiotherapy, Government Medical College, Thiruvananthapuram on an outpatient basis once every 21 days for 6–8 cycles. Patients satisfying inclusion criteria were enrolled into the study until the required sample size was attained. During the first visit, after obtaining informed consent, semi-structured questionnaire and chemotherapy protocol were filled. Adherence to the chemotherapy schedule was enquired by telephonic interview with the patient on the day before each cycle. Department of radiotherapy follows revised response criteria for malignant lymphoma to assess the disease response rate. Disease response rate is the percentage of patients who attain positive response to treatment at a specific time. During the visit at 1 month after completion of chemotherapy regimen, these criteria were used to categorize response of each patient and disease response rate is calculated.

Rituximab-CHOP regimen with adjuvant medications was as follows: (1) Inj. Ondansetron 8 mg IV single dose, (2) Inj. Paracetamol 1 g IM single dose 30 min before Rituximab, (3) Inj. Pheniramine maleate 25 mg single IV bolus 30 min before Rituximab, (4) Inj. Dexamethasone 16 mg single IV bolus 30 min before Rituximab, (5) T. Prednisolone 20 mg 3-0-2 for 5 days. First dose given 30 min before Rituximab, (6) Inj. Rituximab 375 mg/m^2 IV infusion in 500 ml 0.9% NaCl, (7) Inj. Cyclophosphamide 750 mg/m^2 IV bolus Methodology 34, (8) Inj. Doxorubicin 50 mg/m^2 IV infusion over 30 min, (9) Inj. Vincristine 1.4 mg/m^2 IV over 5–10 min, (10) Inj. Ranitidine 50 mg IV single dose, (11)T. Allopurinol 300 mg oral od for 1–2 cycles, (12) T. Pantoprazole 40mg bd for 10 days, and (13) T. Ondansetron 8 mg tds for 8 days.

Statistics

Data are analyzed using descriptive statistics (proportions and percentages).

RESULTS

The present study was conducted in the Department of Radiotherapy, Government Medical College, Trivandrum between January 2015 and January 2016 in 32 patients

with the diagnosis of histopathologically proven *de novo* follicular lymphoma. They were prescribed Rituximab-CHOP regimen. Patients who were adequately staged and who have not received any other disease specific treatment were included in the study. Assessment of disease response was done and results analyzed. Majority of patients showed positive response to treatment.

Stage-Wise Distribution of Study Subjects

As given in Table 1, follicular lymphoma is staged based on Ann Arbor staging system adapted for non-Hodgkin's lymphoma. Majority of patients belonged to stage III or IV.

Distribution of CD Positivity among Study Subjects

All patients included in this study were CD 20 positive by immunohistochemistry.

Categorization of Study Subjects Based on FLIPI Score

FLIPI is a scoring system based on which patients can be categorized into high, intermediate and low risk groups and 5 year and 10 year overall survival percentages have been predicted. As given in Table 2, five patients belonged to low risk, ten patients to intermediate risk, and 17 patients to high risk group.

Disease Response

Disease response was categorized based on Revised Response Criteria for malignant lymphoma comparing physical examination and imaging studies done before start of chemotherapy and 1 month after completion of chemotherapy. As per these criteria, there can be complete remission/partial remission/stable disease/relapsed disease (after complete remission) or progressive disease (after partial remission/stable disease). The present study assesses only the initial response to treatment which is done 1 month after completion of chemotherapy regimen. Hence, patients are categorized to have attained complete remission/partial remission/stable disease only. They may remain in remission or stable disease or they may develop relapse (after complete remission) or progression of disease (after partial remission or stable disease). At 1 month after completion of chemotherapy, 13 patients attained complete remission, 16 patients attained partial remission, and three patients had stable disease.

Table 1: Number of patients in each stage of follicular lymphoma

Stage	Frequency	Percentage
I	0	0
II	4	12.5
III	18	56.25
IV	10	31.25
Total	32	100

Positive and Negative Response to Treatment

In a study by Papaioannou *et al.*, complete remission and partial remission are together categorized as positive response to treatment and the rest as negative response to treatment.[4] Disease response rate is the percentage of patients who attain positive response to treatment at a specific time. In this study, 1 month after completion of chemotherapy, 29 patients showed positive response to treatment and three patients showed negative response to treatment. As per this study, disease response rate to RCHOP regimen for follicular lymphoma is 90.625% at 1 month after completion of chemotherapy. All patients whose response was assessed using Positron Emission Tomography (PET) scan showed positive response to therapy.

DISCUSSION

Rituximab-CHOP regimen has the highest efficacy ever described with any chemotherapy in follicular lymphoma.[5] Addition of Rituximab to chemotherapy has made significant improvements in response rate and progression-free survival of patients with follicular lymphoma.[6-8] This study was undertaken to study the response of follicular lymphoma to R-CHOP regimen. Secondary objective was to assess the tolerability of patients to this regimen by listing the adverse events leading to non-compliance to R-CHOP regimen followed by causality assessment and grading of toxicity. According to FLIPI, patients with age <60 years have better prognosis when compared to those with age >60 years. In the present study, 24 patients were <60 years and eight patients were more than 60 years of age. Age range of patients included in this study was from 37 to 83 years which is same as that in a study by Overman *et al.*[9] FL has slight female preponderance.[10,11] The present study included 25 males and seven females. In this study, 87.5% patients had

Table 2: Risk categorization of patients

Risk category	Predicted 5year OS (%)	Predicted 10 year OS (%)	Frequency	Percentage
Low	91	71	5	15.625
Intermediate	78	51	10	31.25
High	52	59	17	53.125
Total				100

stage III or IV disease compared to a study by Overman *et al*. which had 80 % patients with stage III or IV disease.[9] All patients in this study were CD 20 positive by immunohistochemistry, as in a study by Czuczman *et al*.[12] In this study, according to FLIPI score, 16% patients were low risk, 31% intermediate risk, and 53% high risk. In a study by Jacobs *et al*., the corresponding figures were 25%, 33% and 42%.97. In the present study, CR rate after R CHOP was 40.625%. In a study by Jacobs *et al*., complete response rate was 40%.[13]

Limitations of the Study

This study was a prospective observational study. For better assessment of efficacy, a randomized controlled trial is preferable. Sample size was small. Larger sample size will yield a better picture of FL in Indian population. Response was assessed based on CT scan in majority of cases. We cannot determine if residual enlarged nodes by size criteria contain viable lymphoma. PET is a better alternative as a functional imaging tool for staging and response assessment of lymphomas.

REFERENCES

1. World Health Organization. World Cancer Report 2014. Ch. 5.13. Geneva: World Health Organization; 2014.
2. Marcus R, Sweetenham JW, Williams ME. Lymphoma: Pathology, Diagnosis and Treatment. 2nd ed. Cambridge, United Kingdom: Cambridge University Press; 2013. p. 1-4.
3. Domingo-Domènech E, González-Barca E, Estany C, de Sevilla AF. Combined treatment with anti CD20 and CHOP in relapsed advanced stage follicular lymphomas. Haematologica 2002;87:1229-30.
4. Papaioannou D, Rafia R, Rathbone J, Stevenson M, Woods HB, Stevens J. Rituximab for the first-line treatment of stage III-IV follicular lymphoma (review of technology appraisal no. 110): A systematic review and economic evaluation. Health Technol Assess 2012;16:1-253. iii-iv.
5. Coiffier B. Rituximab therapy in malignant lymphoma. Oncogene 2007;26:3603-13.
6. Van Oers MH, Klasa R, Marcus RE, Kimby E, Gascoyne RD, Jack A, *et al*. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized Phase 3 intergroup trial. Blood 2006;108:3295-301.
7. Salles G, Mounier R, de Guibert S, Morschhauser F, Doyen C, Rossi JF, *et al*. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: Results of the GELA-GOELAMS FL2000 study. Blood 2008;112:4824-31.
8. van Oers MHJ, Klasa R, Marcus RE, Wolf M, Kimby E, Gascoyne RD, *et al*. Rituximab maintenance improves clinical outcome of relapsed or resistant follicular non hodgkin lymphoma in patients with and without rituximab during induction: results of a prospective randomised phase 3 intergroup trial. Blood 2006, 108: 3295-301.
9. Overman J, Feng L, Pro B, McLaughlin P, Hess M, Samaniego F, *et al*. The addition of rituximab to CHOP chemotherapy improves overall and failure-free survival for follicular grade 3 lymphoma. Ann Oncol 2008;19:553-9.
10. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: Clinical features of the major histologic subtypes. Non-Hodgkin's lymphoma classification project. J Clin Oncol 1998;16:2780-95.
11. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, *et al*. World Health organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: Report of the clinical advisory committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 1999;17:3835-49.
12. Czuczman MS, Weaver R, Alkuzweny B, Berlfein J, Grillo-Lopez AJ. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus chop chemotherapy: 9-year follow up. J Clin Oncol 2004;22:4711-6.
13. Jacobs SA, Swerdlow SH, Kant J, Foon KA, Jankowitz R, Land SR, *et al*. Phase II trial of short course RCHOP followed by 90Y-ibrutumomab tiuxetan and extended rituximab in previously untreated follicular lymphoma. Clin Cancer Res 2008;14:7088-94.

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Original Article

Assessment of Spirometric Parameters in Patients with Type 2 Diabetes Mellitus in a Tertiary Care Hospital of North East India: A Cross-sectional Study

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Abstract

Background: Diabetes mellitus (DM) is a group of metabolic disorders occurs due to defects in insulin secretion, insulin action, or both. Pulmonary complications of DM have been poorly characterized with conflicting results. Because of its large reserve, substantial loss of the microvascular bed can be tolerated without developing any signs and symptoms. As a result, pulmonary diabetic microangiopathy may be under recognized clinically.

Aims and Objectives: The aim of the study was to estimate the changes spirometric parameters in Type 2 DM (T2DM) patients and to assess the effect of duration of the disease and the status of glycemic control of the patients on their pulmonary function.

Materials and Methods: Spirometry was done in 120 T2DM patients aged between 30 and 60 years, attending the Diabetes and Nutritional clinic of A.G.M.C over a period of 3 months by using Spirometry –model SPM –A. The spirometric parameters recorded were- forced vital capacity (FVC), forced expiratory volume in 1st s (FEV_1), FEV_1 to FVC ratio (FEV_1/FVC), forced expitatory flow at 25–75% of the lung volume (FEF_{25-75}), peak expiratory flow rate and maximum voluntary ventilation. Data were entered in computer using Microsoft Excel. Descriptive statistics and other suitable statistical tests such as χ^2 test were used as per applicability. A probability value <0.05 was considered as significant.

Results: Statistical analysis was carried out using SPSS software and results were statistically analyzed and correlated. FVC (P = 0.012) and FEV_1 (P = 0.024) values were significantly decreased in diabetic patients. However, FEV1/FVC values were significantly increased (P = 0.042) in patients with T2DM. Significant correlation was found between FVC and FEV_1/FVC with duration of illness and FEV_1/FVC with glycosylated hemoglobin.

Conclusion: T2DM, a systemic disease, also affects lungs causing restrictive type of ventilatory changes probably because of glycosylation of connective tissues, reduced pulmonary elastic recoil, and inflammatory changes in lungs. As spirometry is a reliable, valid, and simple test, the diabetics are suggested to undergo pulmonary function testing periodically.

Key words: Forced expitatory $flow_{25-75}$, Forced expiratory volume in 1st s, FEV_1/FVC, Forced vital capacity, Peak expiratory flow rate and maximum voluntary ventilation, Spirometry, T2DM

INTRODUCTION

Diabetes is the most common metabolic disorder which is on increasing trend globally.[1] It is accompanied by wide spread biochemical, morphological, and functional abnormalities which may precipitate certain complications that affect the neural, cardiovascular, renal systems, and also organs and tissues such as skin, liver, collagen, and elastic fibers. The microvascular complications appear early, within 5–10 years and macrovascular complications appear within 15–20 years from the onset of diabetes.[2]

Pulmonary complications of diabetes mellitus (DM) have been poorly characterized with conflicting results. The alveolar capillary network in the lung is a large microvascular unit and may be affected by microangiopathy.

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However, because of its large reserve, substantial loss of the microvascular bed can be tolerated without developing dyspnea. As a result, pulmonary diabetic microangiopathy may be under recognized clinically. It has also been suggested that pulmonary dysfunction may be one of the earliest measurable non-metabolic alterations in diabetes.[3]

The respiratory diseases associated with diabetes may result in changes in pulmonary volumes, diffusion, and elastic properties of lungs as well as the performance of respiratory muscles chronic low-grade inflammation, decrease in pulmonary diffusion capacity. Several histopathological changes are also seen in diabetics. Few researchers suggest that diabetes could lead to the development of pulmonary complications due to collagen and elastin changes. While others suggest that increased non-enzymatic glycosylation of proteins and peptides of the extracellular matrix at chronic high circulating glucose levels may also have an important role in the pathological changes of the lungs in DM patients. This process results in impaired collagen and elastin cross linkage with a reduction in strength and elasticity of connective tissues. These abnormalities in the structural components can lead to the development of abnormalities in the pulmonary function such as a reduction in the vital capacity, total lung capacity, lung compliance, reduction of central, and peripheral airflows, acceleration of the ageing process.[4-6] Alteration in the pulmonary connective tissue by thickening of the alveolar and capillary endothelial basement membranes might cause modifications of alveolar surfactants altering its function and pulmonary microangiopathy which brings about reduction in diffusing capacity and the muscle endurance.[7]

Spirometry is a basic, widely used pulmonary function test. It typically assesses the lung volumes and flow and is ideally suited to describing the effects of obstruction or restriction on lung function. It is now regarded as an integral component of any respiratory medical surveillance program.[8,9]

Pulmonary damage at an early stage in patients with DM is subclinical and rarely present with complaints.[10] Spirometry non-invasively quantifies the physiological reserves in a large micro-vascular bed that is not clinically affected by diabetes. Lung functions may provide useful measures of the progression of systemic microangiopathy in diabetic patients.[11]

Thus, this study was undertaken to assess the pulmonary function in patients with Type 2 DM and to correlate the lung function with duration of diabetes and to find out whether it is obstructive or restrictive pattern.

MATERIALS AND METHODS

Primary Objective

The primary objetive of the study was to estimate the changes in spirometric parameters in Type 2 DM (T2DM) patients.

Secondary Objectives

The secondary bjectives of the study are as follows:

1. To assess the effect of duration of the diabetes on spirometric parameters
2. To assess the effect of glycemic status of the patients on their spirometric values.

A hospital-based and cross-sectional study was done in 120 Adults with T2DM attending diabetes and nutritional clinic OPD of Agartala Government Medical College (AGMC) and Govind Ballabh Pant (GBP) Hospital, Agartala. Ethical clearance was obtained from the Ethical Committee of AGMC and GBPH. The study subjects were evaluated by general history, clinical examination, and blood glycosylated haemoglobin (HbA1c) level. The study was conducted between the periods from October 2022 to November 2022.

Inclusion Criteria for the Cases

The following criteria were included in the study:

1. Patients aged between 30 and 60 years
2. Diagnosed cases of T2DM as given by the American diabetes association
    a. Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/l (200 mg/dl) or
    b. FBS ≥7.0 mmol/l (126 mg/dL) or
    c. HbA1c ≥6.5% or
    d. PPBS ≥11.1 mmol/l (200 mg/dL) during an OGTT.
3. No recent history of respiratory illness
4. Cooperative and willing to participate in the study.

Exclusion Criteria for the Cases

The following criteria were excluded from the study:

1. Already existing chronic complications of diabetes such as retinopathy, neuropathy, and nephropathy
2. Present or past history of respiratory illness that might affect lung function such as bronchiectasis, tuberculosis, bronchial asthma, interstitial lung diseases, and COPD
3. History of occupational exposure to any substance that could affect lung function
4. Individuals with unacceptable spirometry techniques. Unacceptable spirometry means any effort in which FEV1 or FVC could not be measured due to:
    - Cough
    - Sub maximal effort

- Obstructed teeth
- Air escape
- Effort sustained for <6 s duration
- Failure to attain a volume time curve
- Lack of understanding the procedure
- Recent surgery
- Diabetics who have cardiac and liver disease on history (history of jaundice) and clinical examination (icterus, ascites, hepatomegaly, and spleenomegaly) basis

5. Known case of cardiovascular disorders such as hypertension, coronary artery disease, and congestive cardiac failure
6. Presence of any other concomitant diseases as per previous records disrupting cardiovascular homeostasis such as thyroid disorders, pheochromocytoma, chronic renal failure due to any cause, respiratory disorders, and dyselectrolytaemia
7. History of smoking, alcoholism, or intake of any drugs such as vasodilators, diuretics, anti-arrhythmic, beta-blockers, alpha-agonist, or Alpha-blockers
8. Those who are not willing to participate in the study.

Study Tools

- Spirometry-model SPM –A
- Sphygmomanometer-Mercury deluxe BP apparatus manufactured by diamond allied products SSI no- UAN-MH33A0014692
- Stethoscope
- Height measuring stand-Bioplus; height −200 cm
- Weighing machine
- Investigating materials and Kit for estimation of blood sugar and HbA1c.
- Case study format.

Recording of Spirometry

After taking detailed history and relevant clinical examination, informed consent was taken. Then, we recorded the anthropometric parameters such as height and weight and body mass index (BMI) was calculated. After demonstrating the technique for carrying out spirometry, subjects were made to undergo the tests.

All the tests were conducted according to American Thoracic Society/European Respiratory Society guidelines in a quiet room in sitting position by the Spirometer SPM-A for 3 times at every 15 min interval and best of three was taken into account.

The participants were made to relax in comfortable loose clothing. They were made to sit comfortably and nose clip was applied on the nose. The spirette was kept in the mouth with the lips sealing around it and was instructed to breathe calmly and care was taken not to block or bite the spirette. They were asked to do tidal breathing and fill the lungs completely and then asked to exhale as hard and fast as possible until the lungs were completely empty and inhale as hard and fast as possible till the end of the test. This test was repeated 2–3 times and the best value was taken for the result.

The forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), peak expiratory flow rate (PEFR), FEV1/FVC, FEF 25–75%, and maximum voluntary ventilation (MVV) were recorded.

RESULTS

A total of 120 T2DM patients had participated in this study. Among them 37% were female and 63% were male as shown in Figure 1. Mean age group was 42.24 ± 5.46 years. Age-wise distribution of study participants is shown in Figure 2. Mean HbA1c level was 9.51 ± 2.65%. HbA1c level of the patients is shown in Figure 3. Duration of disease among the study participants is shown in Figure 4. The lung function parameters FVC, FEV_1, $FEF_{25–75}$, PEFR and MVV all were found to be decreased among the study participants [Table 1]. FEV_1/FVC values were increased among Type 2 DM patients [Table 1]. However, changes in FVC ($P = 0.012$), FEV_1 ($P = 0.024$), and FEV_1/FVC ($P = 0.042$) were statistically significant. Mean values of the spirometric parameters are shown in Figure 5 and Table 1. A Significant negative correlation ($r = −0.3208$, $P = 0.004$) was found between FVC and duration of diabetes as shown in Figure 6. There was a significant positive correlation ($r = 0.090$, $P = 0.012$) between FEV_1/FVC and HBA1c level as shown in Figure 7.

DISCUSSION

DM is accompanied by wide spread biochemical, morphological, and functional abnormalities. Pulmonary

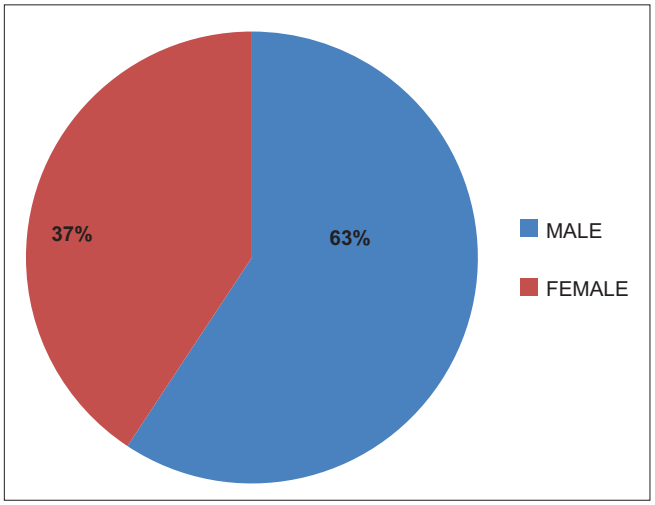

Figure 1: Gender-wise distribution of study participants

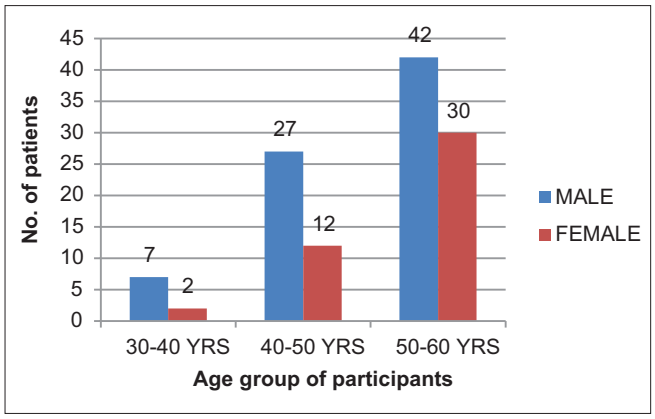

Figure 2: Age-wise distribution of patients

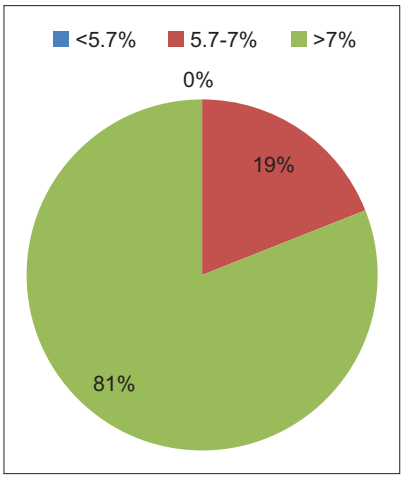

Figure 3: HbA1c of the study participants

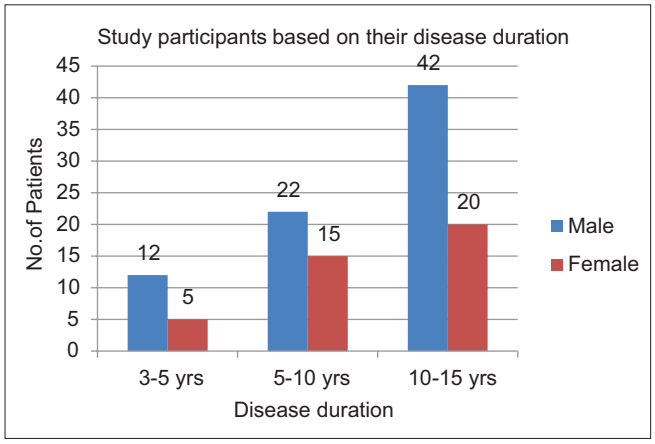

Figure 4: Disease duration of the study participants

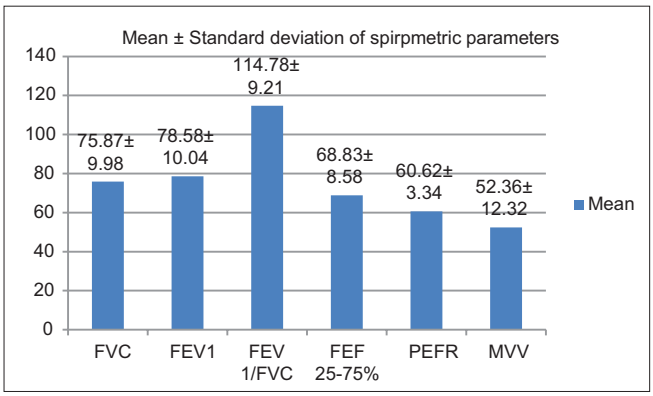

Figure 5: Mean ± Standard deviation of the spirometric parameters

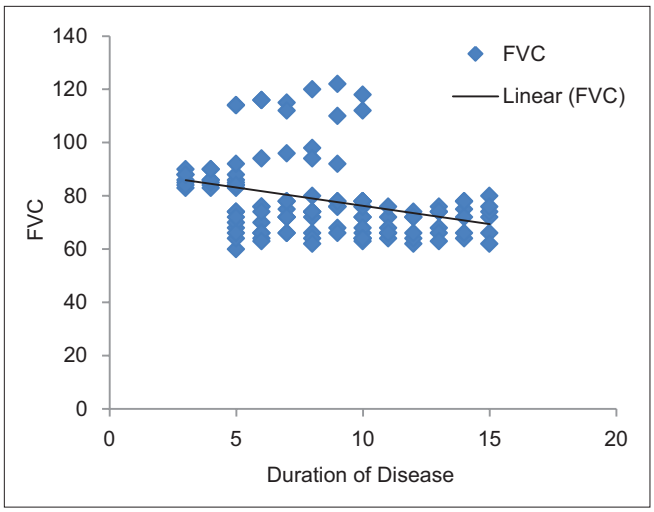

Figure 6: Correlation of forced vital capacity with duration of disease

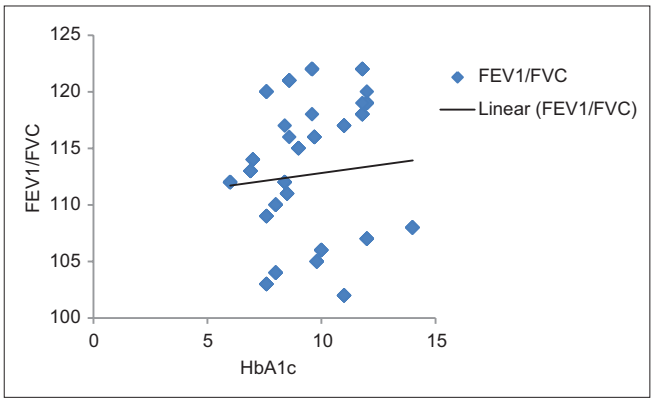

Figure 7: Correlation between forced expiratory volume in 1/forced vital capacity and HbA1c

complications of DM have been poorly characterized with conflicting results. In our study we have found that there was a significant reduction in FVC, and FEV_1 values in patients with T2DM. However, FEV_1/FVC was significantly higher in those patients. These findings indicated restrictive type of changes in lung function among Type 2 diabetic people. We have also found significant negative correlation of FVC with duration of diabetes and a positive correlation between FVC/FEV_1 and HBA1c level.

Finding of this study was in accordance with Davis *et al.*, who conducted a large community based study in Western Australia in Type 2 diabetic patients and demonstrated that

Table 1: Spirometric parameters of the study participants

S. No.	Spirometric parameters	Mean±SD	*P*-value
1.	FVC	75.87±9.98	0.012*
2.	FEV1	78.58±10.04	0.024*
3.	FEV1/FVC	114.78±9.21	0.042*
4.	FEF 25–75%	68.83±8.58	0.752
5.	PEFR	60.62±3.34	0.236
6.	MVV	52.36±12.32	1.302

**P* value is significant (<0.05). FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1st s, FEF: Forced expitatory flow, PEFR: Peak expiratory flow rate, MVV: Maximum voluntary ventilation

FVC, FEV_1, and PEF were decreased in Type 2 diabetic patients.[12] Meo *et al*., in their study on Saudi diabetic patients showed significant reduction in FVC, FEV_1, and PEF, as compared to their matched controls. They also showed a strong association with a dose-effect response of duration of disease and decreased pulmonary functions impairment in their diabetic patients and observed restrictive pattern of airway disease when the duration of diabetes is longer than 10 years.[13]

Rosenecker *et al*. demonstrated that in patients with diabetes, FVC, and FEV_1 declined significantly over the 5-year study period, whereas patients without diabetes did not show a significant decline during this period.[14] In Kanya Kumari *et al*., study spirometric findings showed that as the duration of diabetes increased the restrictive profile was more prominent.[15]

Agarwal *et al*. found spirometric values (FVC, FEV_1, and FEV_1/FVC) were consistently lower in subjects with T2DM. The effect on FVC predicted % was found to be more pronounced in subjects whose duration of DM was more than 5 years.[2] Tangadhuri. *et al*. showed in their study that the pulmonary functions FVC, FEV_1, PEF, and $FEF_{25-75\%}$ were decreased in Type-2DM compared to controls.[16]

A study by van den Borst *et al*. stated that irrespective of BMI, duration of disease, smoking, and glycemic control, there was a statistically significant impairment in pulmonary function of diabetics than in normal individuals.[17] Kumari *et al*. concluded that pulmonary function parameters such as FEV_1 at the 1st s (FEV_1), FVC, FEV_1/FVC, PEFR, and $FEF_{25-75\%}$ had significant changes in diabetic cases than healthy individuals.[15] Yeh HC and Punjabi NM suggested that pulmonary function such as FVC and FEV_1 was significantly lower in diabetics than non-diabetics.[18]

Several histopathological changes in lung tissues were seen in patients with Type 2 diabetes. Some researchers like Ljubic *et al*.[19] showed that diabetes could lead to the development of pulmonary complications due to collagen and elastin changes. While others suggest that increased non-enzymatic glycosylation of proteins and peptides of the extracellular matrix at chronic high circulating glucose levels may also have an important role in the pathological changes of the lungs in DM patients.[11] This process results in impaired collagen and elastin cross linkage with a reduction in strength and elasticity of connective tissues. These abnormalities in the structural components can lead to the development of abnormalities in the pulmonary function such as a reduction in the vital capacity, total lung capacity, lung compliance, reduction of central and peripheral airflows, and acceleration of the ageing process. Alteration in the pulmonary connective tissue by thickening of the alveolar and capillary endothelial basement membranes might cause modifications of alveolar surfactants altering its function and pulmonary microangiopathy which brings about reduction in diffusing capacity and the muscle endurance.

CONCLUSION

Our study showed that pulmonary function was compromised in T2DM and the changes were of restrictive pattern. As the duration of diabetes increases, the restrictive lung impairment becomes more prominent. Therefore, the patients with Type 2 diabetes are needed to undergo pulmonary function testing periodically. Strict glycemic control and regular breathing exercises to strengthen respiratory muscles are necessary to improve the pulmonary function in Type 2 diabetics.

Limitations of the Present Study

The sample size in the present study is relatively small. Also, unknown and subclinical complications, which are unaccounted for, may contribute to spirometric changes.

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REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37:S81-90.
2. Agarwal A, Grover A. Pulmonary function test in patients of Type 2 diabetes mellitus. Int J Res Med Sci 2019;7:2240-45.
3. Nemagouda SK. Spirometric abnormalities in patients with Type 2 diabetes mellitus. J Evol Med Dent Sci 2019;8:3014-8.
4. Kaur S, Agarwal N. Pulmonary function tests in Type 2 diabetes mellitus. Arch Med Health Sci 2016;4:35-9.

5. Shah S, Sonawane P, Nahar P, Vaidya S, Salvi S. Pulmonary function tests in Type 2 diabetes mellitus and their association with glycemic control and duration of the disease. Lung India 2013;30:108-12.
6. Mathew J. Clinical evaluation pulmonary function test in Type II diabetes mellitus. Int Arch Integr Med 2019;6:37-42.
7. Suguna S, Vinodha R. A study of pulmonary function test in Type II diabetes mellitus-spirometry based. Int J Physiol 2018;6:1-6.
8. Rajani M, Manoj DK, Ram R, Achuthan V. Study of pulmonary function tests in Type 2 diabetes mellitus. Pulmonol 2013;15:201.
9. Chidri SV, Vidya G. Assessment of pulmonary functions in Type 2 diabetes mellitus: Its correlation with glycemic control and body mass index. Natl J Physiol Pharm Pharmacol 2020;10:553-6.
10. EI-Azeem AA, Hamdy G, Amin M, Rashad A. Pulmonary function changes in diabetic lung. Egypt J Chest Dis Tuberc 2013;62:513-7.
11. Gajbhiye R, Tambe A. Pulmonary function test in Type II diabetics. Glob J Biol Agric Health Sci 2014;3:20-2.
12. Davis WA, Knuiman M, Kendall P, Grange V, Davis TM. Fremantle Diabetes Study. Glycemic exposure is associated with reduced pulmonary function in Type 2 diabetes: The Fremantle Diabetes Study. Diabetes Care 2004;27:752-7.
13. Meo SA, Al-Drees AM, Arif M, Al-Rubean K. Lung function in Type 2 Saudi diabetic patients. Saudi Med J 2006;27:338-43.
14. Rosenecker J, Hofler R, Steinkamp G, Eichler I, Smaczny C, Ballmann M, *et al*. Diabetes mellitus in patients with cystic fibrosis: the impact of diabetes mellitus on pulmonary function and clinical outcome. Eur J Med Res 2001;6:345-50.
15. Kumari DH, Nataraj SM, Devaraj HS. Correlation of duration of diabetes and pulmonary function tests in type 2 diabetes mellitus patients. Int J Biol Med Res 2011;2:1168-70.
16. Thangadhurai A. Assessment of pulmonary function tests in Type 2 Dm. IOSR J Dent Med Sci 2018;17:23-6.
17. van den Borst B, Gosker HR, Zeegers MP, Schols AM. Pulmonary function in diabetes: A metaanalysis. Chest 2010;138:393-406.
18. Yeh HC, Punjabi NM, Wang NY, Pankow JS, Duncan BB, Cox CE, *et al.* Cross-sectional and prospective study of lung function in adults with type 2 diabetes: The atherosclerosis risk in communities (ARIC) study. Diabetes Care 2008;31:741-6.
19. Ljubic S, Metelko Z, Car N, Roglic G, Drazic Z. Reduction of diffusion capacity for carbon monoxide in diabetic patients. Chest 1998;114:1033-5.

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Original Article

Histopathological/Cytological Correlation of Cervical Tubercular Lymphadenitis cases with GeneXpert and MGIT TB Culture

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Abstract

Introduction: Tuberculosis (TB) is one of the major health problems in India. India is the second most populous country in the world behind China but India has the maximum number of TB cases worldwide accounting for one fourth of the global TB cases.

Materials and Methods: A hospital-based observational study was undertaken to analyze the sensitivity, specificity, positive predictive value and NPV of nucleic acid amplification assay (GeneXpert) using samples in 86 patients with suspected EPTB and compare with MGIT and histopathology/cytology.

Results: A hospital-based observational study was undertaken to analyze the sensitivity, specificity, positive predictive value, and NPV of Nucleic acid amplification assay (GeneXpert) using samples in 86 patients with suspected EPTB and compare with MGIT and histopathology/cytology. All results are depicted in form of tables in main manuscript.

Conclusion: Rapid TB tests may be the key to worldwide TB control strategies. The high sensitivity and specificity, coupled with its speed and simplicity, make the GeneXpert MTB the most useful tool in the rapid diagnosis of TB. This rapid TB diagnostic test may complement usual methods (conventional microscopy, culture, and histopathology).

Key words: Cervical lymph nodes, Drug culture, Tuberculosis

INTRODUCTION

Tuberculosis (TB) is a disease caused by mycobacterium tuberculosis (MTB) which is a gram positive, aerobic, acid, and alcohol fast bacillus. TB is one of the major health problems in India. India is the second most populous country in the world behind China but India has the maximum number of TB cases worldwide accounting for one fourth of the global TB cases. In 2013, out of the estimated global annual incidence of 9 million TB cases, 2.1 million were estimated to have occurred in India.[1] During recent years, there has been emergence of resistance to multiple drugs in TB bacilli which has become a great threat to public health. When TB bacilli become resistant to both isoniazid and rifampicin or only mono-resistant to rifampicin it is called multidrug-resistant TB (MDR TB).[2] With additional emergence of resistance to 2nd line drugs, that is, to any fluoroquinolone, and to at least one of the three injectable second-line drugs (amikacin, kanamycin, and capreomycin) it becomes Extensive Drug-Resistant TB (XDR TB).[2] According to the World Health Organization (WHO), MDR-TB update 2015 about 5% (in comparison to 3.7% in 2013) of new TB patients in the world have MDR-TB and 9.7% (in comparison to 9% in 2013) of MDR-TB cases also have resistance to two other classes of drugs or extensively drug resistant TB (XDR-TB).[3] Resistance in new TB cases is defined as primary drug resistance, the presence of resistant strains of MTB in patients who have never received anti- TB drugs or who have been treated for <1 month. Resistance in previously treated cases is defined as secondary drug resistance, the presence of a resistant strain of MTB in patients who have received anti-TB drugs in the past or who have been treated for more than 1 month.[4] Drug resistant TB (DR-

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TB) is a manmade problem[5] because of inadequate use of drug, inappropriate prescription and poor adherence or compliance to treatment. These factors permit the selective growth and multiplication of drug resistant strains. The emergence of DR-TB strains is a global problem which poses a serious threat to the best of efforts of prevention and TB control.[6] The WHO reported that DR-TB is increasing in various parts of world as well as in India.[7] TB commonly involves the lungs also known as pulmonary TB but extra-pulmonary sites are also commonly involved. Extra pulmonary TB (EPTB) is a paucibacillary disease and the affected patients are non-infectious. EPTB include[4] lymph node TB, tuberculous pleural effusion, central nervous system TB, spinal TB, abdominal TB, genitourinary TB, pericardial TB, and Skin TB. Extrapulmonary sites could be involved due to any of the following mechanisms: (a) Spread by hematogenous route is the most common mode of disease at extrapulmonary site, (b) reactivation of a pre-existing focus of TB infection (post primary TB), (c) spread due to contiguity like in pleural TB, pericardial TB, gastrointestinal TB, and (d) direct inoculation as seen in skin TB. EPTB and EPTB with MDR TB/XDR TB are a significant health problem in both developing and developed countries.[8] Diagnosis of EPTB in its different clinical presentations remains a true major challenge due to different sites of involvement and paucibacillary nature of the disease. There is scarcity of data regarding EPTB MDR patients and most of the available studies focus on total MDR patients. However details of EPTB MDR subset of patients of total MDR patients and their demographic profile is not clearly studied in the literature. More so drug resistance reported in EPTB is a challenge to diagnosis and management. Due to this fact our study is unique, that is focusing on EPTB MDR patients, their prevalence, demographic details, and associated comorbidities.

TB has been a major global public health problem from times immemorial. WHO estimates shows that globally there are 8.6 million incident cases of TB of which 80% are in 22 countries, with India ranked as the highest burden country.[9]

The diagnosis of pulmonary TB can be obtained from microscopy and culture of a number of different sources including regular sputum, induced sputum, gastric washings, and bronchoscopy. The sensitivity, specificity and diagnostic yield of each of these tests vary widely between studies.[10-16] Sputum induction with hypertonic saline requires additional resource allocation and manpower training, but has been shown to increase the diagnostic yield of sputum examination in several studies.[17-19]

Microbiological diagnosis is the main stay for the effective treatment of pulmonary TB for obtaining the correct sputum sample, patient education is imperative. However, even if the correct sample is expectorated, the bacillary population has to be at least 10000 per milliliter, to get the smear positive for acid fast bacilli (AFB).[20] Moreover, it depends on the previous treatment, default behavior, and effective cough. Difficulties arise when a patient who is suspected of active TB, both clinically and radiologically, does not produce sputum. Harris *et al.* found that 40–60% of patient with active pulmonary TB suspected clinically or radiologically may fail to produce sputum, or when it is available AFB may be negative.[21]

Diagnosis of extrapulmonary TB (EPTB) remains especially challenging since the number of MTB bacilli present in tissues at sites of disease is often low and clinical specimens from deep-seated organs may be difficult to obtain. Histology is time-consuming to undertake and establishing a diagnosis of TB with high specificity remains difficult. Tissue microscopy after special staining is often negative and when mycobacteria are seen, it is impossible to distinguish MTB from nontuberculous mycobacterial disease.

In recent times, attention has been devoted to new nucleic acid amplification diagnostic technologies, due to their rapidity, sensitivity, and specificity. One of the latest systems, the GeneXpert MTB/RIF (Xpert) assay, based on nested real-time PCR and molecular beacon technology, has been shown to be rapid, with a result for TB and RIF drug resistance under 2 h.[22]

Nucleic acid amplification tests for rapid TB diagnosis are increasingly being used. The US CDC recommends that nucleic acid amplification tests be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB.[23] However, no recommendation exists for their use in the investigation of patients suspected of having EPTB as the evidence base is limited.

The Xpert® MTB/RIF assay (Cepheid Inc., CA, USA) marks an important development in the field of rapid molecular TB diagnostics.[24,25] This multifunctional diagnostic platform is an automated, closed system that performs real-time PCR and can be used by operators with minimal technical expertise, enabling diagnosis of TB and simultaneous assessment of rifampicin resistance to be completed within 2 h. Sputum samples can be analyzed with very minimal processing, yielding positive diagnoses in 99–100% of patients with smear-positive pulmonary TB and 57–83% of patients with smear-negative pulmonary TB in clinical evaluation studies.[24] The Xpert MTB/RIF assay was rapidly endorsed by the WHO in December 2010 as a replacement for sputum smear microscopy,

particularly in settings with high rates of HIV-associated TB and multidrug-resistant TB.

Since Xpert MTB/RIF was specifically developed and optimized for testing sputum samples and initial large-scale evaluations were in patients with pulmonary TB, the WHO endorsement specifically applied to the investigation of pulmonary TB. More recently; however, evaluations of the assay have extended to a variety of non-respiratory clinical samples from patients with EPTB. The evidence base for use in the investigation of EPTB remains comparatively weak; however, many more studies assessing a variety of clinical samples other than sputum are therefore needed.

Aims and Objectives

The objectives are as follows:

- To analyze the sensitivity, specificity, positive predictive value and negative predictive value (NPV) of nucleic acid amplification assay (GeneXpert) using samples in patients with suspected EPTB
- To compare with MGIT and histopathology/cytology in suspected EPTB patients.

MATERIAL AND METHODS

A hospital-based observational study was undertaken to analyze the sensitivity, specificity, positive predictive value and NPV of nucleic acid amplification assay (GeneXpert) using samples in 86 patients with suspected EPTB and compare with MGIT and histopathology/cytology.

Study Site

A tertiary health-care institute in a metro city.

Study Population

Patients with cervical lymphadenopathy visiting the outpatient department of surgery and pulmonary medicine.

Study Design

This was a hospital-based observational study.

Study Duration

18 months.

Sample Size

86 patients.

The customized excel sheet for sample size calculation prepared from standard references (Patrikar)[33] was used to calculate sample size for present study. With reference to the study of Hillemann *et al.*,[34] the sensitivity and specificity of GeneXpert in diagnosing EPTB (prevalence was 22% in similar institute) published in article were 77% and 98%, respectively. At 20% precision the estimated sample sizes are 78. Assuming non response rate of 10% the corrected sample size is 78 + 7.8 = 86. The sample size was selected using simple random sample.

Inclusion Criteria

The following criteria were included in the study:

1. Adults >18 years male/female
2. Patients giving consent.

Exclusion Criteria

The following criteria were excluded from the study:

1. Pregnant lady
2. Children
3. Patient not giving consent.

Methodology

All patients with cervical lymphadenopathy visiting the outpatient department of surgery and pulmonary medicine. After obtaining informed written consent their evaluation included detailed history and clinical examination performed with investigations including Gene Expert, MGIT and histopathology, cytology/fnac, and Mantoux test.

Suspected case of EPTB

Clinical, Radiological (XRAY/USG/CT), Mantoux test

Biopsy done-

1. Histopathology/cytology
2. MGIT
3. GeneXpert

Laboratory Methods

Each sputum and BAL samples received in the lab from the centers as per the collection and transportation policy of the laboratory were divided into three parts; one part was immediately tested using GeneXpert, second part used for ZN smear microscopy and third part for MGIT BACTEC 320 liquid culture and performed on same day. Only one sample either BAL or sputum from a single patient was divided and processed. For liquid culture as much as sample was taken after sending for GeneXpert and ZN stain but it should be checked that volume remaining should not be <2 mL for processing.

GeneXpert testing was performed according to the manufacturer's instructions. Sample reagent was added to untreated sputum and BAL at a ratio of 2:1, manually agitated and kept for 10 min at room temperature, then shaken again and kept for 5 min; 2 mL of the inactivated material was transferred to the test cartridge and inserted into the test platform. Only electronic results were used for comparison. Direct Smear microscopy was performed to investigate presence of AFB with the second part of

the specimen using conventional ZN staining method. Slides showing red colored AFB were taken as positive and negative slides were those without any AFB.

Third part was processed using the N-acetyl-L cysteine-sodium hydroxide method (NaOH) as per the manufacturer's instructions, cultured on MGIT media and incubated in MGIT BACTEC 320 liquid culture system. NaOH is a decontaminating agent and also acts as emulsifier and NALC acts as a mucolytic agent and also reduces the concentration of NaOH required. When the tubes were flagged positive by the system, ZN staining and culture on 5% sheep blood agar were performed from the tube directly to see any contamination as per the manufacturer's instructions. All tubes were checked for positivity till 42 days. Mycobacterium other than TB (MOTT) and MTB testing from positive culture tubes were done by rapid immunochromatography test kit using MPT 64 antigen according to the manufacturer's instructions.

Statistical Analysis

Quantitative data are presented with the help of Mean and Standard deviation. Comparison among the study groups is done with the help of unpaired *t*-test as per results of normality test. Qualitative data are presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Fisher test, student "*t*" test and Chi-square test. $P < 0.05$ is taken as significant.

Pearson's Chi-squared test

$$X^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}$$

Where X2 = Pearson's cumulative test statistic.

Oi = an observed frequency;

Ei = an expected frequency, asserted by the null hypothesis;

n = the number of cells in the table.

Results were graphically represented where deemed necessary.

Appropriate statistical software, including but not restricted to MS Excel, SPSS ver. 20 will be used for statistical analysis. Graphical representation will be done in MS Excel 2010. Sensitivity and specificity were estimated using standard formula.

OBSESRVATIONS AND RESULTS

A hospital-based observational study was undertaken to analyze the sensitivity, specificity, positive predictive value, and NPV of Nucleic acid amplification assay (GeneXpert) using samples in 86 patients with suspected EPTB and compare with MGIT and histopathology/cytology.

Distribution of Patients According to Age

Majority of the patients (42.1%) were from the age group of 31–40 years followed by 25.6% from the age group of 41–50 years, 13.8% from the age group of 51–60 years, 11.6% from the age group of 21–30 years, and 6.9% from the age group of >60 years.

Distribution of Patients According to Gender

There was male preponderance (56.9%) while female patients constituted 43.1% of the study group.

Distribution of Patients According to Symptoms

About 88.4% and 70.9% patients presented with cough and fever, respectively. The other symptoms were breathlessness (51.2%), loss of appetite (44.22%), chest pain (40.7%), hemoptysis (33.7%), and weight loss (16.3%).

Distribution of Patients According to Histopathological Findings

Histopathological findings noted that 19 (22.1%) patients had EPTB while 67 (77.9%) patients showed negative results.

Distribution of Patients According to Cytology Findings

Cytology findings noted that 20 (23.2%) patients had EPTB while 66 (76.8%) patients showed negative results.

Distribution of Patients According to Gene Xpert Findings

Gene Xpert findings noted that 21 (24.4%) patients had EPTB while 65 (75.6%) patients showed negative results.

Distribution of Patients According to MGIT Findings

MGIT findings noted that 22 (25.6%) patients had EPTB while 64 (74.4%) patients showed negative results.

Comparison of Gene X-pert Findings with Histopathological Findings

The sensitivity and specificity of Gene Xpert were calculated at 84.21% and 92.54% respectively. The positive predictive value of Gene Xpert is 76.19% and the NPV is 95.38%.

Comparison of MGIT Findings with Histopathological Findings

The sensitivity and specificity of MGIT were calculated at 78.95% and 89.55%, respectively. The positive predictive value of MGIT is 68.18% and the NPV is 93.75%.

Comparison of Cytology with Histopathological Findings

The sensitivity and specificity of cytology were calculated at 73.68% and 91.04%, respectively. The positive predictive value of MGIT is 70% and the NPV is 92.42%.

Table 1: Distribution of patients according to age

Age (years)	*n*	%
21–30 years	10	11.6
31–40 years	36	42.1
41–50 years	22	25.6
51–60 years	12	13.8
>60 years	6	6.9
Total	86	100

Table 2: Distribution of patients according to gender

Gender	*n*	%
Male	49	56.9
Female	37	43.1
Total	86	100

Table 3: Distribution of patients according to symptoms

Symptoms	*n*	%
Cough	76	88.4
Fever	61	70.9
Breathlessness	44	51.2
Loss of appetite	38	44.2
Chest pain	35	40.7
Hemoptysis	29	33.7
Weight loss	14	16.3

Table 4: Distribution of patients according to Histopathological findings

Histopathological findings	*n*	%
Positive	19	22.1
Negative	67	77.9
Total	86	100

Table 5: Distribution of patients according to Cytology findings

Cytology findings	*n*	%
Positive	20	23.2
Negative	66	76.8
Total	86	100

Table 6: Distribution of patients according to Gene Xpert findings

Gene Xpert findings	*n*	%
Positive	21	24.4
Negative	65	75.6
Total	86	100

Comparison of Various Diagnostic Methods for Diagnosing EPTB

Gene Xpert had highest sensitivity at 84.21% specificity at 92.54%, positive predictive value (PPV) of 76.19% and a NPV of 95.38%. [Tables 1-11].

Table 7: Distribution of patients according to MGIT findings

MGIT findings	*n*	%
Positive	22	25.6
Negative	64	74.4
Total	86	100

Table 8: Comparison of Gene Xpert findings with Histopathological Findings

Gene Xpert	Histopathological	
	Positive (%)	Negative (%)
Positive	16 (18.6)	5 (7.5)
Negative	3 (3.5)	62 (70.4)
Total	19 (22.1)	67 (77.9)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Gene Xpert	84.21	92.54	76.19	95.38

NPV: Negative predictive value, PPV: Positive predictive value

Table 9: Comparison of MGIT findings with histopathological findings

MGIT	Histopathological	
	Positive (%)	Negative (%)
Positive	15 (17.4)	7 (8.1)
Negative	4 (4.7)	60 (69.8)
Total	19 (22.1)	67 (77.9)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MGIT	78.95	89.55	68.18	93.75

NPV: Negative predictive value, PPV: Positive predictive value

Table 10: Comparison of Cytology with Histopathological Findings

Cytology	Histopathological	
	Positive (%)	Negative (%)
Positive	14 (16.3)	6 (7.1)
Negative	5 (5.8)	61 (70.8)
Total	19 (22.1)	67 (77.9)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cytology	73.68	91.04	70	92.42

NPV: Negative predictive value, PPV: Positive predictive value

DISCUSSION

A hospital-based observational study was undertaken to analyze the sensitivity, specificity, positive predictive value and NPV of nucleic acid amplification assay (GeneXpert) using samples in 86 patients with suspected EPTB and compare with MGIT and histopathology/cytology.

Table 11: Comparison of various diagnostic methods for diagnosing Extrapulmonary Tuberculosis

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Gene Xpert	84.21	92.54	76.19	95.38
MGIT	78.95	89.55	68.18	93.75
Cytology	73.68	91.04	70	92.42

NPV: Negative predictive value, PPV: Positive predictive value

Diagnosis of EPTB remains a challenge due to a lack of sensitive conventional laboratory techniques. Therefore, nucleic acid amplification techniques play an important role in rapid and accurate diagnosis.

The Xpert assay has brought about a major change in the speed, simplicity, and accuracy of not only diagnosis of TB but also drug resistance to RIF in TB, which is accepted as a surrogate for MDR-TB. The rapidity and robustness of diagnosis in-turn breaks the chain of transmission in addition to early institution of treatment and improved chances for cure. The utility of Xpert assay in diagnosis of pauci-bacillary TB is the most important contribution of the test. WHO policy document 2013 adopted a GRADE system approach to arrive at recommendations[35] on the diagnostic value of the assay in pulmonary and EPTB.

In the present study, majority of the patients (42.1%) were from the age group of 31–40 years followed by 25.6% from the age group of 41–50 years, 13.8% from the age group of 51–60 years, 11.6% from the age group of 21–30 years, and 6.9% from the age group of >60 years. There was male preponderance (56.9%) while female patients constituted 43.1% of the study group. This is similar to the studies of Ghariani *et al.*,[28] Singh *et al.*,[29] and Sarfaraza *et al.*[31]

Ghariani *et al.*[28] study evaluating the performance of the GeneXpert MTB/RIF test for the detection of MTB observed male-to-female ratio was 0.47 (56/118) in a total of 174 patients. The median age of the patients was 32.3 years.

Singh *et al.*[29] prospective study assessing the performance of GeneXpert in 761 extra-pulmonary and 384 pulmonary specimens from patients clinically suspected ofTB found male: female ratio of 1.06. There were more males in the 15–30 years age group [ratio 1.15] and almost equal in number in 31–60 years age group [1.02].

Sarfaraza *et al.*[31] prospective cohort study determining the association between histopathological and microbiological findings in patients clinically suspected TBLA observed TBLA and malignancy affected young patients (median age 23 years and 22.5 years, respectively), whereas reactive nodes were found in the older age group (median age 47 years; $P < 0.0001$). The majority of TBLA and malignancy patients were female (79.2% and 68.4%, respectively), whereas a higher proportion of patients found to have reactive nodes were male (55%; $P = 0.002$).

In our study, 88.4% and 70.9% patients presented with cough and fever respectively. The other symptoms were breathlessness (51.2%), loss of appetite (44.22%), chest pain (40.7%), hemoptysis (33.7%), and weight loss (16.3%). This is consistent with the study of Sarfaraza *et al.*[31]

Sarfaraza *et al.*[31] prospective cohort study determining the association between histopathological and microbiological findings in patients clinically suspected TBLA observed chronic cough in 83 (27.9%) patients, but only six (2.7%) had concomitant PTB.

Histopathological findings in the present study noted that 19 (22.1%) patients had EPTB while 67 (77.9%) patients showed negative results. This is concordant to the studies of Ghariani *et al.*[28] and Sarfaraza *et al.*[31]

Ghariani *et al.*[28] study evaluating the performance of the GeneXpert MTB/RIF test for the detection of MTB reported histopathology was positive for 121 (69.5%) specimens showing the presence of caseation and epithelioid granulomas.

Sarfaraza *et al.*[31] prospective cohort study determining the association between histopathological and microbiological findings in patients clinically suspected TBLA reported presumed TBLA was diagnosed on the basis of suggestive histopathology in 198 (89.6%) patients.

Cytology findings in our study noted that 20 (23.2%) patients had EPTB while 66 (76.8%) patients showed negative results. This is comparable to the studies of Singh *et al.*,[29] Suzana *et al.*,[36] Ghariani *et al.*,[28] and Bagdia *et al.*[32]

Singh *et al.*[29] prospective study assessing the performance of GeneXpert in 761 extra-pulmonary and 384 pulmonary specimens from patients clinically suspected of TB reported 72 pulmonary and 35 extra-pulmonary samples were culture positive.

Suzana *et al.*[36] study evaluating the use of Xpert MTB/Rif assay in a routine diagnostic mycobacteriology laboratory for the diagnosis of EPTB reported of 494 samples analyzed against culture, 101 were smear positive and 393 were smear negative.

Ghariani *et al.*[28] study evaluating the performance of the GeneXpert MTB/RIF test for the detection of MTB

reported AFB smears were positive for 41 cases (23.6%). Scanty AFB (<10 AFB) were observed in 75.6% of smear-positive specimens. 79 (45.4%) of the 174 specimens tested were culture positive. MTBC was isolated on MGIT and LJ medium in, respectively, 78 (98.7%) and 40 (50.6%) culture-positive samples. Among the 174 samples tested, the Xpert detected the DNA of MTBC in 134 samples (77%). 79 specimens (45.4%) were culture positive 55 (31.6%) being smear negative and 24 (13.8%) being smear positive); 22 (12.6%) were "probable TB" cases; 43 (24.7%) were only histologically/cytologically positive showing necrosis, caseation, or epithelioid granuloma suggestive of "possible TB" cases; and 30 (17.2%) patients had no evidence of TB and were "not TB" cases.

Bagdia *et al.*[32] study comparing various diagnostic methods for EPTB found out of 97 total cases, cytology detected 87 as positive, while ZN stain detected only 9 as positive for EPTB, culture detected 20 as positive for EPTB.

Gene Xpert findings in our study noted that 21 (24.4%) patients had EPTB while 65 (75.6%) patients showed negative results. These findings were consistent with the studies of Singh *et al.*,[29] Ghariani *et al.*,[28] Bagdia *et al.*,[32] and Sarfaraza *et al.*[31]

Singh *et al.*[29] prospective study assessing the performance of GeneXpert in 761 extra-pulmonary and 384 pulmonary specimens from patients clinically suspected of TB reported in pulmonary group Gene Xpert detected TB in 72 culture positive and 114 culture negative patients, while in extra-pulmonary group it detected TB in 35 culture positive and 181 culture negative patients.

Ghariani *et al.*[28] study evaluating the performance of the Gene Xpert MTB/RIF test for the detection of MTB observed Xpert detected MTBC DNA in 75/79 of culture-positive specimens.

Bagdia *et al.*[32] study comparing various diagnostic methods for EPTB observed out of the 83 cases on Gene Xpert 58 cases were positive for EPTB.

Sarfaraza *et al.*[31] prospective cohort study determining the association between histopathological and microbiological findings in patients clinically suspected TBLA found of these six patients with PTB, three were infectious with sputum smear or GeneXpert positivity and the rest were diagnosed on clinical and radiological grounds.

MGIT findings in the present study noted that 22 (25.6%) patients had EPTB while 64 (74.4%) patients showed negative results. This finding was consistent with the study of Agrawal *et al.*[30]

Agrawal *et al.*[30] retrospective study evaluating the sensitivity of Nucleic acid amplification assay (GeneXpert) and comparing with AFB smear microscopy and AFB culture reported among the 21 Sputum samples, 11 samples were culture and GeneXpert positive, 1 sample was GeneXpert positive. 38 (22%) specimens were culture positive for AFB; 35 (20%) isolates were found to belong to MTB (11 were from sputum specimens, 24 were from BAL specimen), while the remaining 3 (1.7%) strains from BAL samples were identified as mycobacterium other than TB MOTT species. Out of 170 samples, only 14 samples (6 BAL and 8 sputum samples) were found AFB smear positive. All these AFB smear positive samples were culture and GeneXpert positive.

It was observed in the present study that the sensitivity and specificity of Gene Xpert were calculated at 84.21% and 92.54%, respectively. The positive predictive value of Gene Xpert is 76.19% and the NPV is 95.38%. This is in concordance to the studies of Bagdia *et al.*,[32] Suzana *et al.*,[36] Agrawal *et al.*,[30] and Ghariani *et al.*[28]

Bagdia *et al.*[32] study comparing various diagnostic methods for EPTB reported cytology was compared with Gene Xpert out of 56 cases, cytology could detect 53 cases and Gene Xpert could detect 6. Gene Xpert detected 3 cases, which were negative by cytology. Out of these 3 cases, 2 were also negative by culture, ZN stain and LED microscopy.

Suzana *et al.*[36] study evaluating the use of Xpert MTB/Rif assay in a routine diagnostic mycobacteriology laboratory for the diagnosis of EPTB reported of 46 smear-positive, culture-positive samples, and Xpert/Rif detected 45 of 46. Of 55 smear-positive, culture-negative samples, and Xpert MTB/Rif detected 43 of 55. All 43 were diagnosed as TB by the CGS. Of 54 smear-negative, culture-positive samples, 44 of 54 were detected by Xpert MTB/Rif. All 44 were diagnosed as TB by the CGS. Of 339 smear-negative, culture-negative samples, Xpert MTB/Rif detected 59. In total, 58 of 59 were diagnosed as TB by the CGS. Xpert MTB/Rif had a sensitivity of 87% (95% CI 0.79–0.93) and specificity of 73% (95% CI 0.69–0.78). In total, 102 cases detected by the Xpert MTB/Rif assay, whereas mycobacterial culture remained negative. Of these, 101 patients had either clinically or histologically proven TB or a clinical response when treated with ATT Xpert MTB/Rif had a pooled sensitivity of 89% and specificity of 74%.

Agrawal *et al.*[30] retrospective study evaluating the sensitivity of Nucleic acid amplification assay (GeneXpert) and comparing with AFB smear microscopy and AFB culture reported overall sensitivity, specificity, PPV, and NPV of Gene Xpert were 86.8%, 93.1%, 78.5%, and 96%, respectively.

Ghariani *et al.*[28] study evaluating the performance of the GeneXpert MTB/RIF test for the detection of MTB reported sensitivity and specificity of the Xpert assay were 94.9% and 37.9%, respectively, when compared with culture. The sensitivity of the molecular test in smear- positive or -negative and culture-positive samples was, respectively, 100% and 92.7%. The Xpert test detected TB in 77.6% (45/58) of patients with negative cultures and positive histology. Furthermore, the Xpert assay showed 8 positive results in "not TB" cases.

It was observed in our study that the sensitivity and specificity of MGIT were calculated at 78.95% and 89.55%, respectively. The positive predictive value of MGIT is 68.18% and the NPV is 93.75%. Bagdia *et al.*[32] noted similar observations in their study.

Bagdia *et al.*[32] study comparing various diagnostic methods for EPTB observed histopathology detected 10 as positive, while ZN stain detected 5 as positive for EPTB.

It was observed in the present study that the sensitivity and specificity of Cytology were calculated at 73.68% and 91.04%, respectively. The positive predictive value of MGIT is 70% and the NPV is 92.42%. Similar observations were noted in the studies of Bagdia *et al.*[32] and Agrawal *et al.*[30]

Bagdia *et al.*[32] study comparing various diagnostic methods for EPTB found out of 97 total cases, cytology detected 87 as positive, while ZN stain detected only 9 as positive for EPTB, culture detected 20 as positive for EPTB. Culture detected 3 as positive for EPTB.

Agrawal *et al.*[30] retrospective study reported among 156 AFB smear microscopy negative samples, 123 samples were negative for all three methods. In rest 33 AFB smear negative samples, 19 samples were culture and Gene Xpert positive, 9 samples were Gene Xpert positive and culture negative, and 5 samples were culture positive and Gene Xpert negative. In comparison with culture used as gold standard, sensitivity, specificity, PPV, and NPV for Smear microscopy for BAL sample were recorded as 22.2%, 100%, 100%, and 85.3%, respectively.

In our study, Gene Xpert had highest sensitivity at 84.21% specificity at 92.54%, positive predictive value (PPV) of 76.19% and a NPV of 95.38%. This is similar to the studies of Bagdia *et al.*,[32] Agrawal *et al.*,[30] Ghariani *et al.*,[28] Sarfaraza *et al.*,[31] Suzana *et al.*,[36] Meldau R *et al.*,[27] and Vadwai V *et al.*[26]

Bagdia *et al.*[32] study comparing various diagnostic methods for EPTB reported Gene Xpert had highest sensitivity at 85.71% and a NPV of 98.67%, while LED-FM had the highest specificity at 98% (same as of ZN stain) and highest positive predictive value (PPV) of 86.36%. Positivity rate of histopathology was 90.90% while of LED-FM and ZN was 45.45% and of culture was 27.27%. Sensitivity and specificity of histopathology were 66.67% and 33.33%, respectively.

Agrawal *et al.*[30] retrospective study evaluating the sensitivity of Nucleic acid amplification assay (GeneXpert) and comparing with AFB smear microscopy and AFB culture reported of the 170 specimens, 14 samples were positive and 123 specimens were negative by all three methods used. Among 170 samples, 42 samples (24.7%) were GeneXpert TB positive. Among the 149 BAL samples, 22 samples were culture and GeneXpert positive, 8 samples were GeneXpert positive, and 5 samples were only culture positive. GeneXpert assay had an overall sensitivity of 86.8% and for BAL sample 81.4% for PTB, which is superior to that of smear microscopy (overall 36.8% and for BAL 22.2%). Overall Specificities of GeneXpert and smear microscopy were 93.1% and 100%, respectively. For smear negative samples, sensitivity and specificity of GeneXpert was 79.1% and 93.1%, respectively. For smear positive cases, sensitivity was 100%.

Ghariani *et al.*[28] study evaluating the performance of the GeneXpert MTB/RIF test for the detection of MTB reported sensitivity and specificity of Xpert assay when compared with smear microscopy, culture results and histological findings were 87.5% and 73.3%, respectively. Positive predictive value (PPV) was 94%, whereas the NPV was 55%.

Sarfaraza *et al.*[31] prospective cohort study determining the association between histopathological and microbiological findings in patients clinically suspected TBLA reported microbiological evidence was positive in a minority with Gene Xpert, mycobacterial culture, and AFB smear positivity, and was seen in 90 (32.6%), 72 (26.6%), and 34 (12.5%), respectively. The sensitivity of smear, culture, and Gene Xpert was found to be 12.7%, 30.7%, and 33.2%, respectively, when compared with histopathology suggestive of TB. Gene Xpert was positive for MTB in 44 (65.7%) culture-positive cases and 38 (19.6%) culture-negative cases. 16 Gene Xpert-positive, 11 culture-positive, and six AFB smear-positive patients had a reactive cytology.

Suzana *et al.*[36] study evaluating the use of Xpert MTB/Rif assay in a routine diagnostic mycobacteriology laboratory for the diagnosis of EPTB reported compared to culture, pooled sensitivity and specificity of Xpert MTB/Rif were 89% and 74%, respectively. When Xpert MTB/Rif was compared to the CGS, pooled sensitivity and specificity were 62% and 100%, respectively, for fluids. Xpert MTB/

Rif specificity was 95% for CSF, 83% for tissue, 27% for pus, 59% for LN and 90% for fluids.

Meldau R *et al*.[27] prospective cohort study evaluating the performance of the Xpert MTB/RIF assay, and other diagnostic biomarkers, with suspected pleural TB reported Xpert MTB/RIF sensitivity and specificity (95% CI) was 22.5% (12.4–37.6) and 98% (89.2–99.7), respectively, and centrifugation did not improve sensitivity (23.7%).

Vadwai V *et al*.[86] study on diagnostic accuracy assessments of smear and culture results and clinical, radiological, and histological findings reported sensitivity of the Xpert assay was 81% (228/283 specimens) (64% [89/138] for smear-negative cases and 96% [139/145] for smear-positive cases), with a specificity of 99.6%. The sensitivity was found to be high for the majority of specimen types (63–100%) except for cerebrospinal fluid, the sensitivity of which was 29% (2/7 specimens). The Xpert test correctly identified 98% of phenotypic rifampin (RIF)-resistant cases and 94% of phenotypic RIF-susceptible cases. Sequencing of the 6 discrepant samples resolved 3 of them, resulting in an increased specificity of 98%.

CONCLUSION

Rapid TB tests may be the key to worldwide TB control strategies. The high sensitivity and specificity, coupled with its speed and simplicity, make the GeneXpert MTB the most useful tool in the rapid diagnosis of TB. This rapid TB diagnostic test may complement usual methods (conventional microscopy, culture, and histopathology). Diagnosis of EPTB is challenging due to the paucibacillary nature as well as atypical clinical presentations. Its diagnosis should hence be made by considering more than one diagnostic methods.

REFERENCES

1. Zumla A, George A, Sharma V, Herbert RH, Baroness Masham of Ilton; Aaron Oxley, *et al*. The WHO 2014 Global tuberculosis report--further to go. Lancet Glob Health 2015;3:e10-2.
2. Balaji V, Daley P, Anand AA, Sudarsanam T, Michael JS, Sahni RD, *et al*. Risk factors for MDR and XDR-TB in a tertiary referral hospital in India. PLoS One 2010;5:e9527.
3. WHO. Multidrug-Resistant Tuberculosis (MDR-TB) 2015 Update. Available from: https://www.who.int/tb/challenges/mdr/mdr_tb_factsheet.pdf [Last accessed on 2022 Nov 23].
4. Gothi D, Joshi JM. Clinical and laboratory observations of tuberculosis at a Mumbai (India) clinic. Postgrad Med J 2004;80:97-100.
5. Kant S, Maurya AK, Kushwaha RA, Nag VL, Prasad R. Multi-drug resistant tuberculosis: An iatrogenic problem. Biosci Trends 2010;4:48-55.
6. Sharma SK, Mohan A. Multidrug-resistant tuberculosis: A menace that threatens to destabilize tuberculosis control. Chest 2006;130:261-72.
7. World Health Organization. Multidrug and Extensively Drug-Resistant TB (M/XDR-TB): 2010 Global Report on Surveillance and Response. Geneva: World Health Organization; 2010. p. 57.
8. Maurya AK, Kant S, Nag VL, Kushwaha RA, Dhole TN. Trends of anti-tuberculosis drug resistance pattern in new cases and previously treated cases of extrapulmonary tuberculosis cases in referral hospitals in Northern India. J Postgrad Med 2012;58:185-9.
9. Global Tuberculosis Report 2013. p. 6. Available from: https://www.apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf [Last accessed on 2022 Nov 23].
10. Merrick ST, Sepkowitz KA, Walsh J, Damson L, McKinley P, Jacobs JL. Comparison of induced versus expectorated sputum for diagnosis of pulmonary tuberculosis by acid-fast smear. Am J Infect Control 1997;25:463-6.
11. Pai M. The accuracy and reliability of nucleic acid amplification tests in the diagnosis of tuberculosis. Natl Med J India 2004;17:233-6.
12. Dickson SJ, Brent A, Davidson RN, Wall R. Comparison of bronchoscopy and gastric washings in the investigation of smear-negative pulmonary tuberculosis. Clin Infect Dis 2003;37:1649-53.
13. Larson JL, Ridzon R, Hannan MM. Sputum induction versus fiberoptic bronchoscopy in the diagnosis of tuberculosis. Am J Respir Crit Care Med 2001;163:1279-80.
14. De Gracia J, Curull V, Vidal R, Riba A, Orriols R, Martin N, *et al*. Diagnostic value of bronchoalveolar lavage in suspected pulmonary tuberculosis. Chest 1988;93:329-32.
15. Menzies D. Sputum induction: Simpler, cheaper, and safer-but is it better? Am J Respir Crit Care Med 2003;167:676-7.
16. Norrman E, Keistinen T, Uddenfeldt M, Rydström PO, Lundgren R. Bronchoalveolar lavage is better than gastric lavage in the diagnosis of pulmonary tuberculosis. Scand J Infect Dis 1988;20:77-80.
17. Al Zahrani K, Al Jahdali H, Poirier L, René P, Menzies D. Yield of smear, culture and amplification tests from repeated sputum induction for the diagnosis of pulmonary tuberculosis. Int J Tuberc Lung Dis 2001;5:855-60.
18. Bell D, Leckie V, McKendrick M. Use of the induced sputum procedure in the investigation of smear-negative pulmonary tuberculosis. Clin Infect Dis 2004;38:1504-5.
19. Conde MB, Loivos AC, Rezende VM, Soares SL, Mello FC, Reingold AL, *et al*. Yield of sputum induction in the diagnosis of pleural tuberculosis. Am J Respir Crit Care Med 2003;167:723-5.
20. Katoch VM. Newer diagnostic techniques for tuberculosis. Indian J Med Res 2004;120:418-28.
21. Harries AD, Mphasa NB, Mundy C, Banerjee A, Kwanjana JH, Salaniponi FM. Screening tuberculosis suspected using two sputum smears. Int J Tuberc Lung Dis 2000;4:36-40.
22. Helb D, Jones M, Story E, Boehme C, Wallace E, Ho K, *et al*. Rapid detection of *Mycobacterium tuberculosis* and rifampin resistance by use of on-demand, near-patient technology. J Clin Microbiol 2010;48:229-37.
23. Centers for Disease Control and Prevention. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. MMWR Morb Mortal Wkly Rep 2009;58:7-10.
24. Lawn SD, Nicol MP. Xpert(R) MTB/RIF assay: Development, evaluation and implementation of a new rapid molecular diagnostic for tuberculosis and rifampicin resistance. Future Microbiol 2011;6:1067-82.
25. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, *et al*. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 2010;363:1005-15.
26. Vadwai V, Boehme C, Nabeta P, Shetty A, Alland D, Rodrigues C. Xpert MTB/RIF: A new pillar in diagnosis of extrapulmonary tuberculosis? J Clin Microbiol 2011;49:2540-5.
27. Meldau R, Peter J, Theron G, Calligaro G, Allwood B, Symons G, *et al*. Comparison of same day diagnostic tools including Gene Xpert and unstimulated IFN-γ for the evaluation of pleural tuberculosis: A prospective cohort study. BMC Pulm Med 2014;14:58.
28. Ghariani A, Jaouadi T, Smaoui S, Mehiri E, Marouane C, Kammoun S, *et al*. Diagnosis of lymph node tuberculosis using the GeneXpert MTB/RIF in Tunisia. Int J Mycobacteriol 2015;4:270-5.
29. Singh UB, Pandey P, Mehta G, Bhatnagar AK, Mohan A, Goyal V, *et al*. Genotypic, phenotypic and clinical validation of GeneXpert in extra-pulmonary and pulmonary tuberculosis in India. PLoS One 2016;1:e0149258.
30. Agrawal M, Bajaj A, Bhatia V, Dutt S. Comparative study of GeneXpert with ZN stain and culture in samples of suspected pulmonary tuberculosis. J Clin Diagn Res 2016;10:DC09-12.

31. Sarfaraza S, Iftikharb S, Memon Y, Zahir N, Hereker FF, Salahuddin N. Histopathological and microbiological findings and diagnostic performance of GeneXpert in clinically suspected tuberculous lymphadenitis. Int J Infect Dis 2018;76:73-81.
32. Bagdia M, Bijwe S, Hirani N, Joshi A, Chowdhary A, Agrawal M, *et al*. Lab diagnosis of extra pulmonary tuberculosis: Comparison of histopathology, cytology, ZeihlNeelsen stain and light emission diode microscopy with culture and nucleic acid amplification tests. Int J Cur Res Rev 2018;10:8.
33. Patrikar S. In: Bhalwar R, editor. Text book of Public Health and Community Medicine. 1st ed. New Delhi: Department of Community Medicine, AFMC, Pune and WHO India Office; 2009.
34. Hillemann D, Rusch-Gerdes S, Boehme C, Richter E. Rapid molecular detection of extrapulmonary tuberculosis by the automated GeneXpert MTB/RIF system. J Clin Microbiol 2011;49:1202-5.
35. Sharma SK, Mohan A. Multidrug-resistant tuberculosis. Indian. J Med Res 2004;120:354-76.
36. Suzana S, Ninan MM, Gowri M, Venkatesh K, Rupali P, Michael JS. Xpert MTB/Rif for the diagnosis of extrapulmonary tuberculosis-an experience from a tertiary care centre in South India. Trop Med Int Health 2016;21:385-92.

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