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REVIEW ARTICLE

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Original Article

Clinicopathological Correlation of Cervical Carcinoma: A Tertiary Hospital-based Study

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Abstract

Objectives: This study is conducted to assess the various predisposing factors for cancer cervix and to correlate the clinical and pathological finding using cervix histopathology.

Background: Cervical cancer is the third most common cancer in women worldwide accounting for 9% of all female cancer and 9% death in female due to cervical cancer. We studied 150 cases of cervical carcinoma with different clinical presentations and correlated them with histopathological findings in tertiary hospital in Aurangabad, Maharashtra.

Materials and Methods: A total of 150 cases histopathologically diagnosed as cervical cancer over a period of 1 year were considered for the study. Clinical details of the patient were noted with the help of semi-structured pro forma. The data were analyzed and *P* value calculated.

Results: Of 150 patients, 88 had moderately differentiated squamous cell carcinoma, 24 poorly differentiated, and 32 well differentiated. Adenocarcinoma numbered only six. 98 cases were in the age group of 40–59 years, 39 in the age group of 60–80 years, and 13 in 20–39 years. All six cases of adenocarcinoma were seen in 40–59 years. 96 presented with white discharge, 68 with bleeding per vagina, and 58 had constitutional symptoms. Most of the patients with adenocarcinoma presented with bleeding per vagina. 98 were in Stage 3B, 40 in Stage 2B, 5 in 4A, and 7 in 1B.

Conclusions: Screening of cervical cancer must be done in women with white discharge per vagina.

Key words: Cancer cervix, Clinicopathological correlation, Histopathology, Maharashtra, India

INTRODUCTION

Carcinoma of cervix is the most common cancer responsible for about 5% of all cancer deaths in women worldwide.[1] It is the 5th deadliest cancer in women. There are 1.7 million cases in developing world.[1]

It affects about 16 per 10,000 women in a year and kills 9 per 100,000 per year.[1] In India, 134,000 were detected to have cervical cancer, of which 72,825 women died of cervical cancer.[2] India accounts 1/5 of the burden of cervical cancer worldwide. According to the WHO, 80% of all cases occur in developing countries[3] because prevention programs are either not exist or poorly implemented. Unlike most other malignancies, cancer cervix is easily preventable. Pap smear is easy, simple, and effective screening tool for the detection of early epithelial cell abnormalities.

Women's knowledge level, motivation for screening, and other psychological factors determine her health-seeking behavior.[4] Relative risk of each histological type of invasive cervical cancer is increased with increasing number of sexual partner, young age at first intercourse, increasing parity, increased duration of OC pills use, and smoking.[5]

Human papillomaviruses have emerged as the principal sexually transmitted causal agent in the development of the cancer of uterine cervix in women.[6] Worldwide, the incidence of cervical cancer is approximately 510,000 new cases annually, with approximately 288,000 deaths

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worldwide. The incidence rises in 30–34 years of age and peaks at 55–65 years of age with median age of 38 years.[7]

MATERIALS AND METHODS

The cases were collected from the tertiary care government cancer hospital, Aurangabad, for a period of 1 year. Clearance of ethical board obtained from the institutional ethical committee. A total number of 150 cases histopathologically diagnosed cervical cancer were considered for the study. All details from the patient were taken with the help of semi-structured pro forma. Detailed history about symptoms, menstrual history, systemic examination, local per speculum, and per vaginal examination was done for staging cancer cervix. The data were analyzed with the help of MATLAB software.

RESULTS

A total of 150 cases were analyzed for histopathological type, age parity, symptoms, clinical diagnosis, and clinical staging. Of 150 patients, majority were moderately differentiated squamous cell carcinoma (88) followed by well-differentiated carcinoma (32) and poorly differentiated carcinoma (24). Adenocarcinoma cervix was only six cases [Table 1]. Highest cases were noted in the age group of 40–59 years (98 cases) followed by 60–80 (39 cases) and 20–39 years (13 cases). All six cases of adenocarcinoma were seen between 40 and 59 years [Table 1].

Maximum number of cases was noted in women who had 4–6 children. Hence, it is obvious that multiparty (more than three) is significant risk factor for cancer cervix [Table 2].

White discharge was the most common complaint noted in 96 of 150 accounting 64%. 68 of 150 presented with bleeding per vagina (45.33%) and 58 of 150 had constitutional symptoms of malignancy as back pain, weight loss, and loss of appetite. Most of the patient of adenocarcinoma presented with bleeding per vagina and white discharge per vagina [Table 3].

All the suspected cases of cancer cervix were diagnosed as carcinoma by histopathology. Staging was done by standard protocol for staging. Of 150 patients, 98 (65.33%) were in Stage 3B (tumour extends to pelvic wall), 40 (26.66%) in Stage 2B (tumour with parametrial invasion), 5 (3.33%) in Stage 4A (tumor invades mucosa of bladder or rectum and/or extends beyond true pelvic), and 7 (4.66%) in Stage 1B (clinically visible lesion confined to cervix or microscopic lesion stromal invasion of 3–5 mm depth with 7 mm width) [Table 4].

Table 1: Age distribution in various histological types of cervical cancer

Histopathological type	Age group in years (%)			Total cases (%)
	20–39	40–59	60–80	
Adenocarcinoma	0	6	0	6 (0.04)
WDSCC	1 (3.12)	24 (75)	7 (21.87)	32 (100)
MDSCC	8 (9.09)	56 (62.5)	24 (27.27)	88 (100)
PDSCC	4 (16.66)	12 (50)	8 (33.33)	24 (100)
Total	13 (8.66)	98 (65.33)	39 (26)	150 (100)

*WDSCC: Well-differentiated squamous cell carcinoma, MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma

Table 2: Distribution of parity in cervical carcinoma

Histopathological type	Parity (%)				Total (%)
	1–3	4–6	6–10	>10	
Adenocarcinoma	4 (66.66)	2 (33.33)	0	0	6 (100)
WDSCC	11 (34.37)	20 (62.5)	1 (3.12)	0	32 (100)
MDSCC	44 (50)	41 (46.59)	3 (3.40)	0	88 (100)
PDSCC	10 (41.66)	14 (58.33)	0	0	24 (100)
Total	69 (46)	77 (51.33)	4 (2.66)	0	150 (100)

WDSCC: Well-differentiated squamous cell carcinoma, MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma

Table 3: Clinical signs in various histopathological types of cervical cancer

Clinical signs	Histopathological types of cervical carcinoma (%)				Total
	Adenocarcinoma	WDSCC	MDSCC	PDSCC	100%
WDPV	2 (2.08)	14 (14.58)	64 (66.66)	16 (16.66)	96
BPV	4 (5.88)	21 (30.88)	34 (50)	9 (13.23)	68
PMB	1 (4.16)	3 (12.5)	15 (62.5)	5 (20.83)	24
CS	2 (3.44)	17 (29.31)	25 (43.10)	14 (24.13)	58
MPV	0	0	0	1 (100)	1
PCB	0	9 (26.47)	15 (44.11)	10 (29.41)	34
IM	0	4 (33.33)	6 (50)	2 (16.66)	12
Others	3 (7.14)	8 (19.04)	19 (45.23)	12 (28.57)	42

WDSCC: Well-differentiated squamous cell carcinoma, MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma

Maximum number of cases were in Grade 3 as can be shown in Table 5.

As it can be Seen in Table 6, Maximum Number of Patients in our Study were Treated with Irradiation due to Advanced Stage at Time of Diagnosis.

DISCUSSION

Carcinoma of cervix is the most common cancer responsible for about 5% of deaths in women worldwide. Its ranking in causing death in women worldwide has decreased in the past 50 years from 5th to 8th due to early detection of precancerous lesions.[1] It has been estimated that 5 yearly

Table 4: Distribution of cervical carcinoma in various clinical stages at the time of diagnosis

Histopathological type	Stages of cervical cancer (%)				Total (100%)
	1B	2B	3B	4A	
Adenocarcinoma	0	0	6 (100)	0	6
WDSCC	5 (15.62)	8 (25)	19 (59.32)	0	32
MDSCC	2 (2.27)	25 (28.40)	61 (69.31)	0	88
PDSCC	0	7 (29.16)	12 (50)	5 (20.88)	24
Total	7 (4.66)	40 (26.66)	98 (65.33)	5 (33.33)	150

WDSCC: Well-differentiated squamous cell carcinoma, MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma

Table 5: Distribution of grades in 150 patients

Grade	Number (%)
1	5 (3.33)
2	34 (22.66)
3	100 (66.66)
4	11 (7.33)

Table 6: Distribution of patients according to the mode of treatment

Modality of treatment	Number (%)
Surgery	7 (4.66)
Irradiation	143 (95.33)
Combined surgery and irradiation	2 (1.33)

screening should prevent 84% of invasive cervical cancer and 3 yearly screening will prevent 91%.[1]

About 80% of new cervical cancer cases occur in developing countries like India, which reports approximately one-fourth of world's cases of cervical cancer each year.[2] Incidence of cervical cancer in urban India is decreasing due to more awareness in the urban educated women. Women's sexual habits can increase the risk for cervical cancer as having sex at early age, having multiple sexual partners.

Majority of cervical cancers are squamous cell carcinoma. The lesion arises from squamocolumnar junction and may be by keratinizing or non-keratinizing type (well-differentiated or poorly differentiated carcinoma). Studies have shown that 80–90% of cervical carcinoma are squamous cell carcinoma and rest of them constitute adenocarcinoma.[3] Adenocarcinoma of the uterine cervix arises from the endocervical columnar cells and constitutes about 14% of cervical carcinoma.[4]

In the present study, 96% of cases were squamous cell carcinoma, of which majority (61.11%) were moderately differentiated squamous cell carcinomas. Adenocarcinoma constituted only 4% of cases [Table 4].

According to our study, maximum number of cases was found in the age group of 40–59 years. Most of studies have observed maximum cases in elder women >40 years of age.[2,4,5] The most common age group involved in carcinoma cervix ranged from 35 to 50 years.[8] One study reported that incidence rises in 30–34 years of age and peaks at 55–65 years.[9]

According to our study, multiparty (more than three children) shows increased risk of malignancy when compared to lesser number of children. Studies show that women having four and above children have increased risk of malignancy.[2,6,7] One study shows that women with three or more births show statistically significant *P* value, suggesting increased risk for cancer cervix.

Most of the time, early cervical cancer, have no symptoms. Vaginal bleeding, post-coital bleeding, or rarely vaginal mass may be presenting features. In case of advanced disease, patient may present with abdominal pain, breathing difficult, and cervical neck mass. Advanced carcinoma can present with loss of appetite, weight loss, fatigue, pelvic pain, leg pain, swollen legs, heavy bleeding from vagina, or rarely leakage of urine or feces from the vagina. White discharge per vagina was the most common complaint in more than 50% of the patient with malignancy in one study.[2,7] In our study, most of the patient presented with white discharge per vagina followed by bleeding per vagina. Bleeding per vagina was the most common presentation in adenocarcinoma [Table 3].

In the present study, all of the cases were clinically diagnosed as cervical cancer was confirmed by histopathology in present study majority of the patient 98(65.33%) were in stage 3B.

In contrast to our result of 3B as the most common presenting staging for cervical carcinoma study by Goellner *et al.* suggested that the most common presenting stage is Stage 1 while kalyni *et al* also suggested 3B is the commonest stage.

Table 5 suggests distribution of patient according to grading. Most of the patients 100 (66.66%) had Grade 3 disease. This coincides with study conducted by Goellner, suggesting that 74.5% of patient having Grade 3 disease.[10]

Table 6 suggesting mode of primary treatment in 150 patients which was mainly radiotherapy because 143 patients presented in Stage 3B and very few patients, that is, seven presented in Stage 1 were treated with surgery.

To conclude, this study suggested that the health measures regarding cervical screening have to be started as early as 25 years because early marriages are common in India. Cervical cancer screening should be included in the National Health Programme. White discharge per vagina at any age should not be neglected as it can be symptom of cancer cervix.

CONCLUSIONS

This study suggested that the health measures regarding cervical screening have to be started at early as 25 years because early marriages are common in India. Cervical screening should be included in national health program. White discharge per vagina at any age should not be neglected.

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Original Article

High-resolution Computed Tomography Lung Spectrum in Symptomatic Adult HIV-positive Patients in Correlation with CD-4 Count

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Abstract

Context: Pulmonary disease accounts for 30–40% of the acute hospitalizations of HIV-positive patients. The CD4 count, an indicator of the severity of immune compromise, is of paramount importance for rendering an appropriate differential diagnosis. High-resolution computed tomography (HRCT) of lung provides detailed visualization of lung parenchyma and can characterize diseases according to pattern and distribution which can help in formulating a differential diagnosis.

Aims: The aims of this study were as follows: (1) To identify the radiological appearance/pattern of HIV-associated infections. (2) To correlate the radiological findings with CD4 count.

Settings and Design: This was a cross-sectional study using sample size of 100 HIV-infected patients conducted at the Department of Radiodiagnosis and Imaging, Gandhi Medical College and Hamidia Hospital, Bhopal.

Materials and Methods: A total of 100 adult HIV-infected patients were scanned with HRCT chest and findings were documented and correlated with their CD4+ counts.

Statistical Analysis Used: Data analysis was done using SPSS 21.0. Two-tailed $P < 0.05$ was considered statistically significant.

Results: TB (70%) was the most common infection followed by bacterial pneumonia (14%) and *Pneumocystis jiroveci* pneumonia (6%). Tuberculosis was found in 29% of advance CD4 count patients and 27% of severe CD4 count patients. Consolidation, airspace nodules, miliary nodules, diffuse ground-glass opacity, and pleural effusion showed significant correlation with CD4 counts.

Conclusions: Incidence of all these manifestations fairly correlates with the decline of CD4 counts. Early and proper diagnosis of these pulmonary complications in patients with HIV infection and lower CD4 counts will help clinicians to develop a focused therapeutic approach in their management.

Key words: AIDS, CD4 counts, Fungal ball, Ground-glass opacity, High-resolution computed tomography, HIV infected, Tuberculosis

INTRODUCTION

From the first descriptions of HIV/AIDS, the lung has been most frequently affected by the disease. Most patients develop a pulmonary complication during a history of HIV infection, mainly of infectious etiology. The first published reports of AIDS appeared in 1981 when five homosexual males in Los Angeles (CA, USA) were diagnosed with *Pneumocystis carinii* (currently, *Pneumocystis jiroveci*) pneumonia. Since then, HIV infection has become a pandemic and remains one of the most important global health problems of the 21st century.

The prevalence of patients with HIV infection continues to increase worldwide. Pulmonary disease accounts for 30–40% of the acute hospitalizations of HIV-positive patients. HIV infection causes alteration in several lines of host defenses in the lung and respiratory tract that

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contributes to an increased risk for lung complications. Many well-described infectious diseases, cancers, and other pulmonary diseases occur with increased frequency in this population.

Worldwide, TB is the major cause of mortality in persons with HIV infection and the World Health Organization (WHO) estimates that TB is the cause of death for 13% of persons who die with HIV/AIDS. The CD4 count, an indicator of the severity of immune compromise, is of paramount importance for rendering an appropriate differential diagnosis. Although all HIV-infected patients are at increased risk of bacterial pneumonia and tuberculosis (TB) compared with the general population, opportunistic infections are uncommon in patients with a CD4 count >200 cells/mm^3. Patients with AIDS with a CD4 count <200 cells/mm^3 are at increased risk for certain infectious pathogens such as *P. carinii* pneumonia (PCP) and atypical mycobacteria. Moreover, some infectious pathogens, such as cytomegalovirus and disseminated fungal and mycobacterial infections, are uncommon in HIV-infected population until CD4 counts fall <100 cells/mm^3. Finally, the change in imaging manifestations of disease and the clinical response to treatment provide important diagnostic information.

High-resolution computed tomography (HRCT) of lung provides detailed visualization of lung parenchyma and can characterize diseases according to pattern and distribution which can help in formulating a differential diagnosis. Hence, my study is intended to document these radiological findings and correlate them with patient's CD4 counts.

MATERIALS AND METHODS

This was hospital-based cross-sectional study done at the Department of Radiodiagnosis, Gandhi Medical College and Hamidia Hospital, Bhopal, using purposive sampling and a sample size of 100 HIV-infected patients with documented CD4+ counts, referred to our department for chest assessment.

All subjects were enrolled with detailed oral and written consent.

This study was approved by ethical and scientific committee of our institute.

Inclusion Criteria

On the basis of clinical presentation and plain radiography, all HIV-positive adult patients of age more than 18 years, who presented with lung disease, were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. <18 years age
2. Pregnant HIV-positive females.

Instrumentation and Technique

All examinations are going to be performed on CT/e Wipro 16 slice GE computed tomography machine.

Technique of scanning

Patient preparation

The procedure and objectives of performing the high-resolution CT scan were explained to patient and written consent of patient was taken. Prior fasting was not advocated as the procedure did not warrant the need for contrast injection. The patient was explained and demonstrated the procedure of breath holding during the acquisition of HRCT scans.

HRCT protocol

Patient position

The patient was kept on gantry table in supine position and scans were taken cephalocaudal in the axial axis. In most instances, scans taken with patients in supine position were adequate. The tomogram or scanogram was first taken, and then, scanning of whole lung is done from apex to the base. Using the following protocol, scans were performed on CT/e Wipro GE scanner.

Collimation = 1 mm
KVp = 120–140
mA = 250

Reconstruction Algorithm

To reduce image smoothening and increase spatial resolution, high spatial frequency algorithm was used. It makes structures appear sharper.

Grouping into CD4+ classes is done according to the WHO's classification of CD4+ immunological profile in adult HIV-infected patients,

1. CD4+ counts >500/μL categorized into none or not significant class.
2. 350–499 as mild.
3. 200–349 as advanced.
4. <200 as severe category.

Complete evaluation of all patients was done in the following format:

- Clinical history and examination.
- Laboratory investigations which include:
  - HIV status, CD4 counts,
  - Routine blood examination,

  - Sputum examinations, pleural fluid analysis, and other available investigations.
- Chest X-ray.

Statistical Analysis

Data analysis was done using SPSS 21.0. Variables were expressed as percentages and comparison was by Chi-square analysis. Two-tailed $P < 0.05$ was considered statistically significant.

Graph 1 reveals frequency distribution of HRCT findings among symptomatic adult HIV-positive patients. Airspace nodules were found positive on HRCT in maximum 65% HIV patients followed by consolidation in 53% of patients. Pleural effusion and lymphadenopathy were also more frequently present in 44% and 41% of patients, respectively.

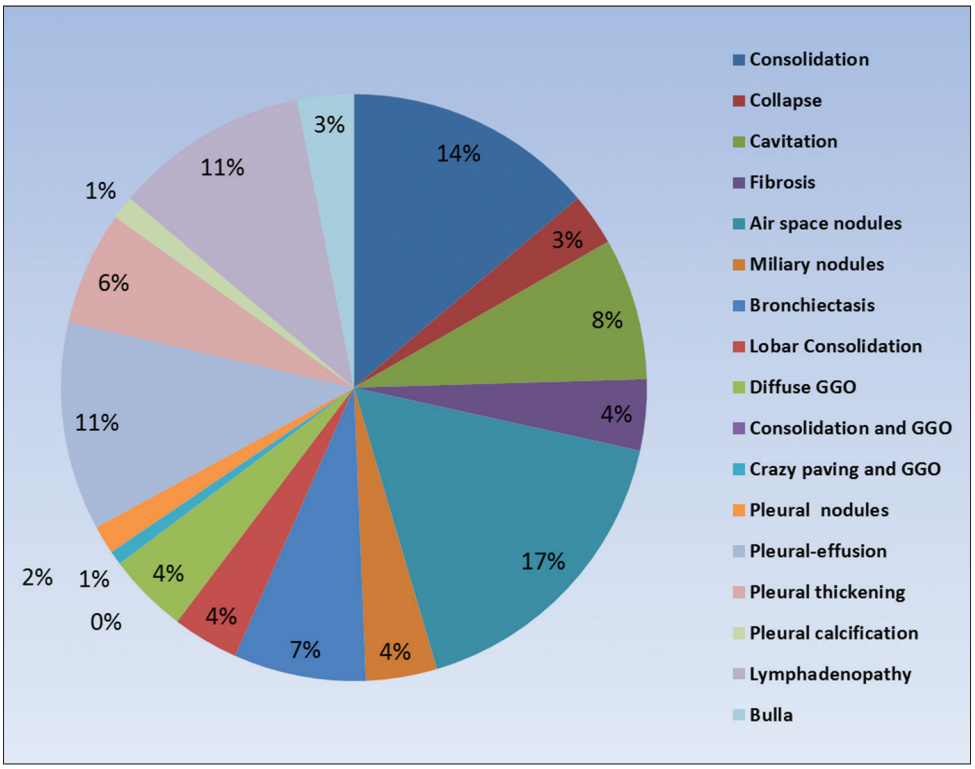
RESULTS

In our study, maximum number of patients was in the age group of 20–40 years. There were 90 patients in the age group of 20–40 years. Of 100 patients included in our study, 65 (65%) were male and 35 (35%) were female. Hence, here, male-to-female ratio was 1.8:1.

Pulmonary Diseases Noted in our Study

- In our study of 100 patients, number of patients diagnosed as having pulmonary TB - 70% of cases.
- Bacterial pneumonia - 14% of cases.
- *P. jiroveci* pneumonia (PJP) - 6% of patients, while 10% of the study did not reveal any significant abnormality.

These diagnoses were made on the basis of imaging findings along with clinical complaints of the patients and laboratory findings.



Graph 1: Frequency distribution of high-resolution computed tomography findings among symptomatic adult HIV-positive patients

Table 1: Association of diagnosis with CD4 count among symptomatic adult HIV-positive patients

Diagnosis	CD4 count				
	Not significant (>500) (%)	Mild (350–499) (%)	Advance (200–349) (%)	Severe (<200) (%)	Total
Normal	4 (40)	6 (60)	0 (0.0)	0 (0.0)	10
TB	0 (0.0)	14 (20)	29 (41.4)	27 (38.6)	70
Bacterial pneumonia	0 (0.0)	4 (28.6)	7 (50.0)	3 (21.4)	14
PCP	0 (0.0)	0 (0.0)	0 (0.0)	6 (100)	6
Chi-square value			61.905		
Significance "*P*" value			0.001 (HS)		

Pulmonary TB

In our study, 70 patients of 100 patients were diagnosed pulmonary TB. The CD4 count in these patients varied from 54 to 460 cells/mm^3 with a mean count of 172 cells/mm^3. The number of patients having CD4 counts <200 cells/mm^3 was 27.

Maximum number (47/70) of patients with pulmonary TB were identified to have nodular opacities. The size of the nodules in all the cases was <1 cm with majority of them being 1–5 mm in size. In about 35 patients, nodules were ill defined, that is, in 74.4% of patients [Figure 1].

Well-defined nodules were noted in six patients only [Figure 2].

- Well-defined nodules with cavitation were noted in six patients.
- Centrilobular pattern of distribution was noted in 71.4% of cases and it was associated with tree in bud opacity in 12.8% of cases.

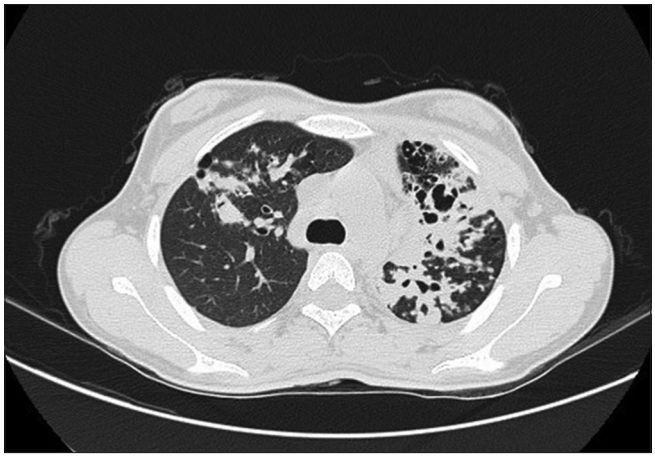


Figure 1: Pulmonary tuberculosis: Scan at carinal level showing consolidation with cavitation in left upper lobe with scattered nodular opacities in bilateral upper lobes.

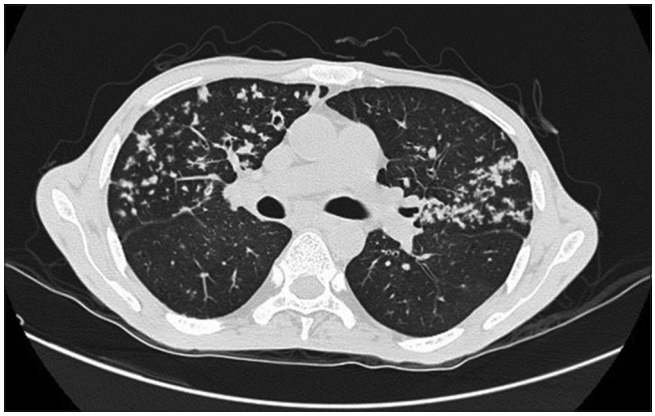


Figure 2: Pulmonary tuberculosis: Scan at subcarinal level shows multiple air space nodules with irregular septal thickening involving bilateral upper lobes

- Miliary pattern was noted 21.4% of the cases [Figure 3].

Thick-walled cavitation was found in 24 patients and thin-walled cavitation was found in six patients [Figure 4]. The location of these cavities was as 16 cases in the right upper lobe, six cases in the right lower lobe, five cases in the left upper lobe, and three cases in the left lower lobe.

About 53.4% of the patients who had cavitation were found to have CD4 count >200 cells/mm^3.

Aspergilloma or fungal ball noted in four cases of tubercular cavity [Figure 5] in which three cases in the right upper lobe and one case in the left upper lobe, CD4 count of all these patients belongs to severe group.

Collapse was noted in 11(15.7%) patients of tuberculosis, out of which 7 in right upper lobe and 4 in left upper lobe.

Lymphadenopathy was noted in 39/70 (55.7%) cases;

- The hilar region in 12 patients,
- Mediastinal in 18 patients,

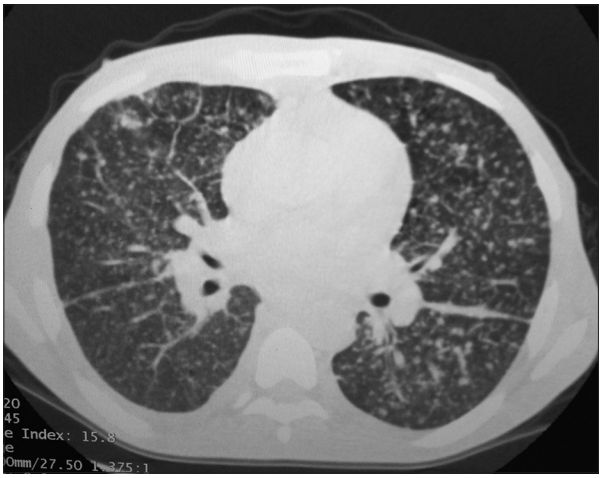


Figure 3: Miliary tuberculosis: Scan at hilar level showing diffuse subcentimetric nodules in bilateral lungs fields

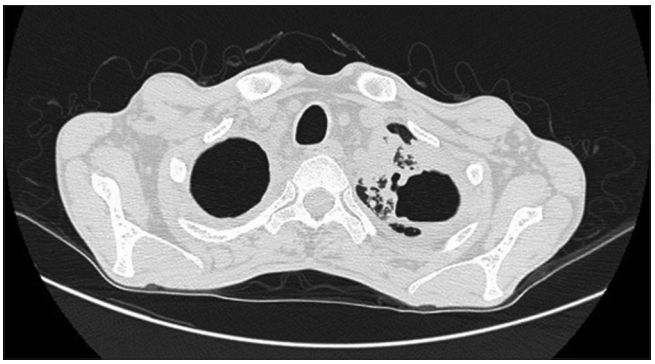


Figure 4: Pulmonary tuberculosis: Scan at the level of lung apices showing bilateral apical bullae with adjacent patchy consolidation in left upper lobe.

- Both hilar and mediastinal lymphadenopathy in nine patients,
- Calcification in lymph nodes was noted in five patients.

Pleural effusion was noted in 33/70, that is, 47.1% of cases. Bilateral pleural effusion was noted in nine patients while 24 patients had unilateral pleural effusion. Among these patients with unilateral pleural effusion, 16 had right-sided pleural effusion while 8 had left-sided pleural effusion [Figure 6].

In 20 of 70 patients with pulmonary TB, bronchiectasis was noted. Bronchial wall thickening was seen in 12 patients with bronchiectasis.

Fibrotic opacities were seen in 15 patients who suggest old healed infective process in addition to the active pathology.

Bulla was seen in 11 (15.7%) cases of TB.

Bacterial infection

In our study, a total of 14 patients were diagnosed to be suffering from bacterial infection. The CD4 count in these patients varied from 108 to 410 cells/mm^3, with a mean count of 212 cells/mm^3. The most common HRCT finding in bacterial infection was lobar consolidation noted in 8 (57.1%) patients followed by focal consolidation, noted in 7 (50%) cases and bronchiectasis was noted in 6 (42.8%) cases [Figures 7 and 8].

PJP

A total of six patients in our study were diagnosed as PJP. The most common HRCT finding was diffuse ground-glass opacities seen in 4 (66.6%) cases. Classic appearance of crazy paving and GGO was seen in two patients [Figure 9]. Few tiny cystic lesions were also noted in two cases in bilateral upper lobes. All of these patients were in severe immunocompromised stage with CD4 counts <200 cells/mm^3, ranging from 20 to 60 cells/mm^3 with a mean count of 32 cells/mm^3. Randomly distributed nodules measured 1–5 mm in size, >5 nodules were noted in five cases.

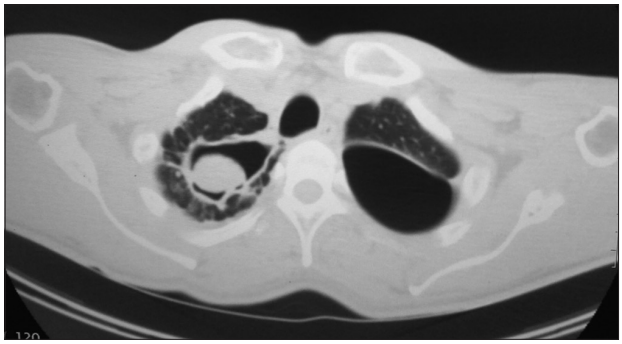


Figure 5: Pulmonary tuberculosis: Scan at the level of lung apices showing irregular cavity in right upper lobe with dependent soft tissue/fungal ball. Bulla in the apicoposterior segment of left upper lobe

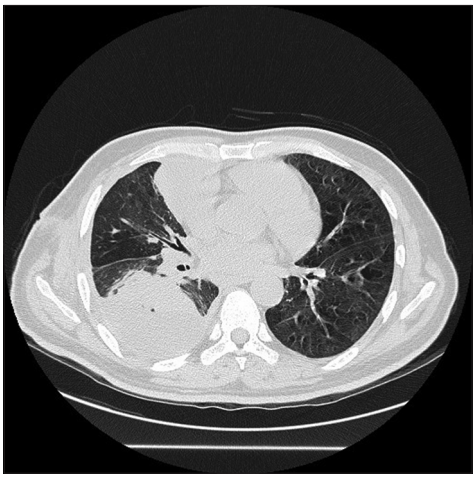


Figure 7: Bacterial pneumonia: Scan at atrial level showing lobar consolidation involving right lower lobe with characterstic absence of air bronchograms

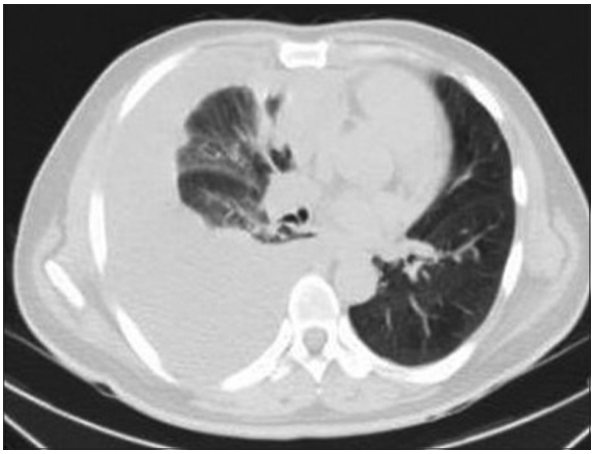


Figure 6: Pulmonary tuberculosis: Scan at aortic root showing moderate right sided pleural effusion with passive collapse of right lower lobe

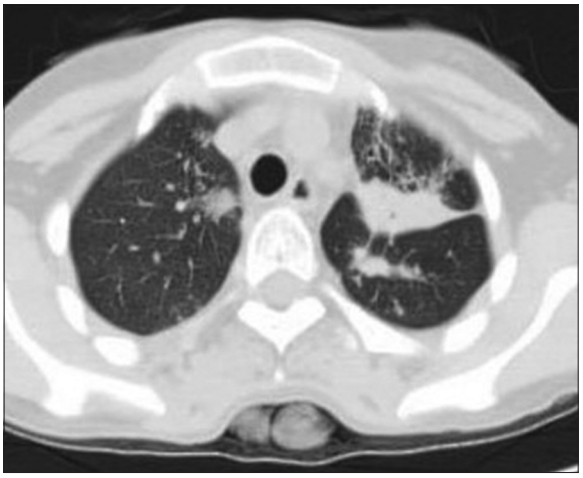


Figure 8: Bacterial pneumonia: Scan at tracheal level showing focal consolidation involving anterior segment of left upper lobe and patchy consolidation in bilateral upper lobes

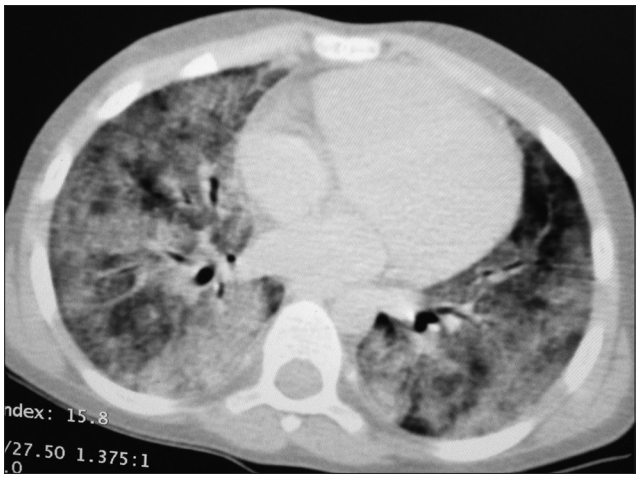


Figure 9: Pneumocystitis Pneumonia: Scan at cardiac ventricles level showing bilateral lower lobes ground glass opacities giving Crazy Paving appearance

DISCUSSION

The disease activity, pattern, degree of involvement, and associated complications were better evaluated with the help of HRCT examination.

According to NACO, HIV estimation 2015:[1]

Total 21.17 lakhs peoples are living with HIV in india in 2015. Incidence of HIV is estimated to 86,300 which is 66% reduction since 2000. AIDS-related death amounts to 67,600, which is 54% reduction since 2007. 10,400 new HIV infections are estimated in children and TB-related deaths among PLHIV amounts to 31,000.

As per the recently released, NACO annual report 2015–2016,[1] HIV prevalence in India is estimated 0.26% (0.22–0.32%) in 2015. In 2015, adult HIV prevalence is estimated 0.30% among males and 0.22% among females.

Age range of cases varied from 18 to 50 years with the maximum number of cases in the age group of 21–30 years (45%) followed by 31–40 years (45%). More than half of the cases (90%) belonged to the age group of 20–40 years. Further, 35% of the cases included in the study were female and 65% were male. This age and sex range nearly corresponds to the data provided by NACO 2015 report.

Of 100 cases in the study, we found among 4% of patient CD4 count were not significant. Among 24% of HIV patients CD4 count were mild. Advance and severe CD4 count were seen in 36% of patients each.

According to the WHO 2014 report, the risk of developing TB is estimated to be between 26 and 31 times greater in people living with HIV than among those without HIV infection. In 2014, there were 9.6 million new cases of TB, of which 1.2 million were among people living with HIV.[2]

Pulmonary TB

TB (70/100) was found to be the most common disease affecting HIV patients in our study.

The WHO reported that in 2014, an estimated 1.2 million (12%) of the 9.6 million people who developed TB worldwide were HIV positive. The African Region accounted for 74% of the estimated number of HIV-positive incident TB cases.[2]

TB disease is the most common opportunistic infection among HIV-infected individuals. Further, it is also known that TB is a major public health problem in India accounts for 20–25% of deaths among PLHIV. It is known that nationally about 5% of TB patients registered under the Revised National TB Control Programme also have HIV infection. In high prevalent states and districts, positivity among TB patients is more than 10% and is as high as 40% in selected districts.[3] Thus, while the country is dealing effectively with HIV burden, TB-associated HIV epidemic is posing a great challenge.

To assess the morphological changes of lung parenchyma, CT is considered as the gold standard.

In our study, 67.1% of patients demonstrated the presence of nodular opacities followed by consolidation (65.7%) which is similar to the study conducted by Naseem *et al.*[4]

In our study, lymphadenopathy was seen in 55.7% cases, which was near similar to study done by Almeida *et al.*

TB lymph nodes are typically markedly enlarged and of low attenuation on CT. Patients with lower CD4 count have an increased incidence of miliary TB, with diffuse, randomly distributed nodules on CT, as found in the study of Keiper *et al.*[6]

Hilar and mediastinal lymph node involvement is commonly seen in HIV positive patients on HRCT.

In pulmonary TB, pleural effusion is a common complication. Effusion is mostly exudative in nature. Unilateral effusion is more common than bilateral. In our study, pleural effusion was found in 47.1% which is nearly similar to a study done by Almeida *et al.*,[5] in which 64.4% of cases had pleural effusion.

Bronchiectasis is generally defined as localized, irreversible bronchial dilatation, often associated with thickening of

the bronchial wall. A bronchus is considered to be dilated if the bronchoarterial ratio exceeds 1.

In a 17 years study conducted in Shanghai, China, pulmonary TB was found to be main cause of bronchiectasis (13.17%). Bronchiectasis is seen in 28.5% of cases in our study.

Emphysematous bulla noted in 12 (17.1%) cases in our study. Emily Clausen *et al*.[7] noted that emphysema was the most common finding (26.4%) in their study.

TB with Fungal Ball

Cavitation was seen in 30 tubercular cases, of which four cases show aspergilloma or fungal ball in the cavity. Guazzelli *et al*.[8] reported six cases of fungal ball in patients with AIDS. In this group, all patients had hemoptysis and TB as the underlying lung disease.

Bacterial Infection

Bacterial infection was found in about 14% of cases. Our study finding is fairly correlating with the study of Hirschtick *et al*.[9]

Lobar consolidation was the most common HRCT finding in bacterial infection seen in 57.1% of patients followed by focal consolidation (50%) and bronchiectasis (42.8%). These findings are consistent with the study of Aviram and Boiselle,[10] in which focal consolidation was observed in approximately 45–60% of patients with pyogenic infection.

Allen *et al*.[11] reported that abnormalities may be detected on HRCT in the absence of any CXR findings these include bronchiectasis and evidence of small airway disease, with ill-defined centrilobular micronodularity and branching structures or tree-in-bud appearance secondary to mucus impaction in the bronchioles. Mosaic attenuation may also be present due to air trapping.

PJP

A total of six patients in our study were diagnosed to be suffering from PJP. The diagnosis was established on the basis of HRCT findings and the clinical profile of the patients along with the findings of bronchoalveolar lavage.

In our study, diffuse ground-glass opacity is seen in all the cases of PCP pneumonia which is fairly correlated with the study of Tasaka *et al*.,[12] and the study of Singh *et al*.[13]

Pneumocystis pneumonia typically presents with extensive ground-glass opacity that may be patchy or diffuse with a central, perihilar, and upper lobe predominance. Accompanying findings may be the thickening of the interlobular septae and rarely the "crazy paving" pattern. Less common manifestations may include the upper lobe lung cysts and areas of consolidation. Differentiating findings from hypersensitivity pneumonitis may be the presence of upper lobe cysts and the associated "crazy paving" pattern. History of immunosuppression, and especially AIDS, favors the diagnosis of pneumocystis pneumonia.

HRCT is very sensitive, the hallmark being ground-glass opacity which is seen in over 90% of the cases and often has a geographic or mosaic distribution, reflecting accumulation of intra-alveolar fibrin, debris, and organisms.

CONCLUSION

Pulmonary tuberculosis was the most common pulmonary manifestation in HIV patients followed by bacterial pneumonia and pneumocystis jiroveci pneumonia and incidence of all these manifestations fairly correlate with the decline of CD4 counts. Early and proper diagnosis of these pulmonary complications in patients with HIV infection and lower CD4 counts will help clinicians to develop a focussed therapeutic approach in their management.

Conventional chest radiography does not rule out the diagnosis of tuberculosis and also less sensitive for other pneumonia,particularly in HIV/AIDS patients and therefore CT scan should be performed in the patients with clinical suspicion of this diseases.

Our study data support the fact that HRCT can be a lot better option than conventional radiographs in complex situations where radiographs cannot differentiate between active disease from old infective/fibrotic changes.

So we recommend that HRCT be used in conjunction with chest radiographs in diagnosis, treatment and follow up of HIV/AIDS patients with pulmonary manifestations. Its non-invasive nature and relatively quicker time of scan makes it a suitable choice in these patients

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Original Article

Foramen Magnum: Morphometry, Possible Variation in the Shape and its Clinical Implication

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Abstract

Introduction: Foramen magnum is midline opening in the occipital bone in the floor of posterior cranial fossa. Morphometry of cranium also helps in establishing the origin of various neurological and skeletal pathologies and also designing various surgical procedures and approaches.

Methods: We conducted a study on 50 dry skull bones in the Department of Anatomy, Government Medical College and Hospital, Chandigarh. The foramen magnum was analyzed for its shape, anteroposterior (AP) diameter, width/transverse diameter (TD), area, perimeter, and FM index. All the measurements were taken with Vernier caliper and were statistically evaluated.

Results: The common shape observed was hexagonal in 45% of cases. The mean of AP and TD was found to be 34.44 mm and 30.46 mm. AP diameter was more than TD. FM index and perimeter were found to be 98.91 mm and 88.44. However, area of foramen magnum was observed to be 745.727 mm^2.

Key word: Foramen magnum, Morphometry, Arnold Chairi malformation

INTRODUCTION

Cranial osteometry has an important place in anthropology and basic medical sciences research.[1-5] It enables identification of species, sex from skeleton, or its remains. Morphometry of cranium also helps in establishing the origin of various neurological and skeletal pathologies and also designing various surgical procedures and approaches.

Foramen magnum is large opening at the lower part of occipital bones. It transmits important structures such as lower end of medulla oblongata, vertebral arteries, meninges, spinal accessory nerve, apical ligament of dens, and membrana tectoria.[6] The cranium base in posterior part of skull is formed of occipital bone and basilar part of sphenoid bone and laterally by mastoid and tympanic part of temporal bone.

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Foramen magnum is midline opening in the occipital bone in the floor of posterior cranial fossa. This foramen is the largest opening in the occipital bone through which the cranial cavity communicates with the vertebral canal. The anterior part or margin of the foramen is formed by the basilar part of occipital bone while the lateral margins are formed by the condylar part of the occipital bone. The posterior margin is formed by the squamous part of the occipital bone. On the inferior surface just in front of its widest diameter, it is encroached on by its medial aspect of the occipital condyles. In most of the subject, it is ovoid in shape and wider in posterior part. Its narrow anterior part lies above the dens of the axis vertebra, its wider posterior part communicates below with the vertebral canal, and through it, the medulla oblongata becomes continuous with the spinal cord.[7] In comparing the different parts of skull, cranium base is thick and it is covered by many structures, protecting it from physical insults.[8]

MATERIALS AND METHODS

For this study on foramen magnum, 50 dry skulls were taken from the Department of Anatomy, Government

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Medical College, Chandigarh. The skull with broken base and deformed shape was not included. The sex and origin of the origin of the skull could not be ascertained as some skulls were part of the skeleton bought from market. The objective is to make a data of various parameters of the foramen magnum in human skull of the region. The various parameters measured were as follows:

1. Sagittal diameter (anteroposterior) from basion to opisthion
2. Transverse diameter (TD) (side to side) maximum diameter in transverse plane
3. Perimeter - length of the periphery of foramen magnum
4. Area of foramen magnum - $1/4 \times \pi \times Td \times APd$
5. Foramen magnum index - $(Td/AP\ d) \times 100$
6. Shape of foramen magnum – oval-, round-, and egg-shaped pentagonal, tetragonal, hexagonal, and irregular.

All the measurements were taken twice and average was recorded. The measurement was taken with the help of Vernier caliper which has minimum error of 0.01 mm. The perimeter was taken with the help of thread which was later measured with the calipers.

The data collected from dimensions of foramen magnum were statistically analyzed.

RESULTS

The results for the shape of foramen magnum [Figure 1] revealed that hexagonal shape is found in maximum skulls, i.e., 45% of cases followed by tetragonal and oval in 17% and 16% of cases. It was round and pentagonal in 4% of cases. The frequency distribution of shape of foramen magnum is depicted in Table 1.

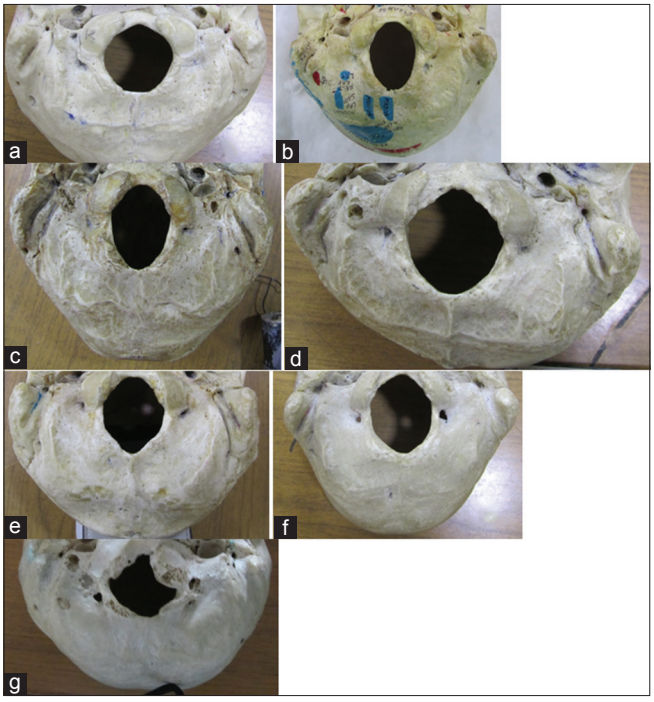

Figure 1: (a) Round, (b) oval, (c) egg shaped, (d) tetragonal, (e) pentagonal, (f) hexagonal, (g) irregular

The mean of anteroposterior (AP) diameter in all shapes was found to be 34.44 mm. The mean TD or width was found to be 30.46 mm. The mean perimeter was 98.91 mm. FM index which was calculated by TD divided by AP diameter was found to be 88.4 mm. The mean area of foramen magnum was 745.727 mm^2.

The mean of all dimensions is shown in Table 2. This gives a good perspective about the mean dimension of the foramen magnum in our region's population.

The measurement of the different shapes separately is also tabulated one by one in the following Tables 4-7.

AP diameter ranged from 29.59 to 34.51 mm. AP diameter was found smallest in oval shape while egg shape had largest AP diameter of foramen magnum [Table 3].

Table 1: Showing frequency distribution of Shape of Foramen magnum (%)

Shape	Frequency	Percentage (%)
Oval	8	15.7
Round	2	3.9
Egg	3	5.9
Pentagonal	2	3.9
Tetragonal	9	17.6
Hexagonal	23	45.1
Irregular	3	5.9

Table 2: Mean of parameters of Foramen magnum

Parameters	Mean
AP	34.44mm
Width	30.46mm
Perimeter	98.91mm
FM index	88.44
Area	745.72mm^2

Table 3: Anteroposterior diameter of foramen magnum

Shape	Number	Mean (mm)	Std.Dev	Median (mm)
Oval	8	29.59	12.22	32.82
Round	2	33.11	3.804	33.11
Egg	3	34.41	2.18	33.56
Pentagonal	2	31.30	1.032	31.30
Tetragonal	9	34.51	2.4653	34.22
Hexagonal	23	33.59	2.88	33.36
Irregular	3	32.01	5.13	31.55

The width of the foramen magnum of different shapes ranged from 23.50 to 29.27 mm. It was found to be maximum in tetragonal shape and minimum in oval shape as shown in Table 4.

The mean of perimeter ranged from 86.49 to 103.05 mm. The standard deviation of perimeter ranged from 3.81 to 36.45 mm. It was found maximum in egg shape and least in oval shape (least AP diameter and width) as shown in Table 5.

FM index ranged from 69.98 to 104.15. It was seen maximum in round shape and least in oval shape as shown in Table 6.

The area of foramen magnum ranged from 63.21 mm to 80.41 mm. It was seen maximum in tetragonal shape and least in oval shape as shown in Table 7.

Table 4: Width of foramen magnum

Shape	Number	Mean (mm)	Std.Dev	Median (mm)
Oval	8	23.50	9.64	26.48
Round	2	27.37	3.27	27.37
Egg	3	27.33	1.22	27.47
Pentagonal	2	27.79	1.407	27.79
Tetragonal	9	29.27	1.59	29.24
Hexagonal	23	28.36	2.141	28.58
Irregular	3	29.01	0.474	28.90

Table 5: Perimeter of foramen magnum

Shape	Number	Mean (mm)	Std.Dev	Median (mm)
Oval	8	86.49	36.45	100.22
Round	2	90.27	10.97	90.27
Egg	3	103.05	3.84	105.13
Pentagonal	2	90.51	3.81	90.51
Tetragonal	9	100.83	6.32	99.34
Hexagonal	23	93.63	20.10	96.45
Irregular	3	98.09	12.79	99.01

Table 6: FM index of foramen magnum

Shape	Number	Mean	Std.Dev	Median
Oval	8	69.98	29.76	76.79
Round	2	104.15	24.35	104.15
Egg	3	79.53	3.70	77.59
Pentagonal	2	88.77	1.56	88.77
Tetragonal	9	85.23	7.69	90.23
Hexagonal	23	85.98	10.65	82.66
Irregular	3	92.01	13.19	91.60

Table 7: Area of foramen magnum (mm^2)

Shape	Number	Mean (mm)	Std.Dev	Median (mm)
Oval	8	712.54	66.32	70.71
Round	2	716.40	166.84	72.64
Egg	3	739.20	74.80	71.67
Pentagonal	2	683.50	57.09	69.30
Tetragonal	9	792.76	66.94	82.76
Hexagonal	23	748.23	88.99	75.87
Irregular	3	730.37	129.21	72.57

DISCUSSION

The occipital bone consists of basilar, lateral, and squamous parts. The basilar, lateral condylar, and lower squamous parts of the occipital are laid down in cartilage, but the upper part of the squama is laid down in membrane. The ossification centers for all these parts appear early in the 3rd month, i.e., for the lower squamous, lateral part, and upper squamous (in that order) in the first few days of the 3rd month followed by that for the basilar part appearing a week later. The supraoccipital has one center. Each lateral occipital has a single center, appearing near the margin of the foramen magnum. The interparietal apparently begins with paired centers, which rapidly merge with each other and with the supraoccipital ossification, but, like most ossification in membrane, the number of centers appears to vary in individuals. There have been described two interparietals and two pre-interparietals, but these seem to be only assumptions based on abnormalities and in any case would probably only have the value of individual variations. The basilar part has a single center, which does not appear to have been seen at any time in an early paired state. The basal ossification extends somewhat backward and outward, and is separated at birth at first by a layer of cartilage from the lateral occipital: It joins this around 6 years. Basioccipital is separated from the basisphenoid by cartilage; result of this is that at birth the bone is in four separate pieces. The tabular and lateral parts unite in the 3rd year and the basal portion joins a few years later. Lateral occipitals form the greatest part of the margin of the foramen, the other elements of the bone only contributing small piece each in front and behind.[9]

The present study is an attempt to see pattern in the various dimensions of foramen magnum in dry adult skulls in North Indians. The knowledge of the anatomy of foramen magnum with all its parameters will be quite helpful in patients with craniocervical/craniovertebral anomalies. The shape and morphology of foramen magnum guide in knowing the cause and devising the treatment of neurological conditions in live born as in Arnold Chiari malformation. The irregularity in the shape of the foramen may be due to developmental anomalies related to bone development and soft tissues at base of cranium.[10]

According to Zaidi *et al.*,[11] foramen magnum shape was oval (64%), hexagonal (24.5%), pentagonal (7.5%), irregular (3.5%), and round (0.5%) cases. In a study conducted by Murshad *et al.*,[12] it was found that foramen magnum was oval shaped in 8.1% of cases. It was round, pentagonal, hexagonal, and irregular in 0.3%, 10.9%, 13.6%, and 13.6%, respectively.

The mean APD and TD in our study were 34.44 mm and 30.46 mm, respectively. Sharma *et al.*[13] found it 47.70 mm and 40.80 mm. Tubs *et al.*[14] observed APD to be 31 mm

and TD to be 27 mm. Murshed *et al.*[12] found it to be 35.9 mm and 30.45 mm. Muthukumar *et al.*[5] found APD and TD to be 33.3 mm and 27.9 mm. Our study findings were similar to the findings of Murshed*et al.*[11]

In the present study, we calculated perimeter, area, and FM index of foramen magnum. The perimeter, area, and FM index were found to be 98.91 mm, 745.72 mm^2, and 88.4, respectively. FM index of the present study was found similar to a study conducted by Sharma *et al.*[13] which was 87.68, respectively. Burdan *et al.*[15] found area and FM index of foramen magnum to be 877.4 mm^2 and 89.34.

CONCLUSION

Knowledge of variation at the craniovertebral junction is important in designing the surgeries at this site. This will help the surgeon in avoiding the damage and unnecessary hemorrhage during the operation. For this variation in morphometry of the foramen magnum giving passage to the spinal medulla becomes even more important. The present study will provide important reference and measurements data might be helpful for anatomists, neurosurgeons, and in other medical fields.

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Original Article

Study of Incidence, Occurrence, Origin, and Histological Types of Eyelid Tumors at Tertiary Care Hospital in Ahmedabad

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Abstract

Background: The aim of the study was to know occurrence, incidence, and various histopathological variants of eyelid tumors. It is incidence with respect to age and to analyse the distribution of tumors in various age group at new civil Hospital, Asarwa, Ahmedabad.

Materials and Methods: A total of 100 cases of eyelid tumors were analyzed retrospectively in a period from May 2008 to November 2010. Cases were studied in detail about general information of the patient including age and sex and gross examination and histological features.

Result: Of 100 tumors, 56 (56%) were benign and 44 (44%) were malignant. Of 56 benign lesions, 41 were in pediatric age group (<18 years) and 15 were in adult patients (>18 years). The common benign lesion seen was nevi (21%) followed by squamous papilloma (12%). The common malignant lesion seen was meibomian gland carcinoma (22%) followed by basal cell carcinoma (12%). Distribution of tumor based on origin on descending order was epithelial origin (33%), adnexal origin (23%), melanocytic origin (22%), and mesenchymal origin (22%).

Conclusion: As eyelid skin is the thinnest and most sensitive skin in our body, it is often the first area in body to show changes occur from sun damage and aging. Skin cancer of the eyelids is relatively common and of several types. Overall, the incidence of benign tumors (56%) was more than malignant tumors (44%) in the present study. Benign tumors were more common in adolescent and young adults. Mean age of benign tumors was 33.83 years. Malignant tumors were more common in elderly. Mean age of malignant tumors was 61.40 years. Overall, sex distribution of benign and malignant tumors is equal in both the sexes.

Key words: Aging, Benign tumors, Malignant tumors, Sun damage

INTRODUCTION

The eyelids are composed of four layers: Skin and subcutaneous tissue, striated muscle (orbicularis oculi), tarsus, and conjunctiva.[1] The eyelid skin is the thinnest and most sensitive skin of our body. As a result, this is often the first area on our face to show changes results sun damage and aging process. Unfortunately, sun damage and other environmental toxins not only cause the skin to age but can also cause serious damage. Skin cancer of the eyelids is relatively common and of several types. As tumors in other organs, tumors of the eyelid can be classified according to their tissue or cell of origin and as benign or malignant.[2,3] Benign epithelial lesions, basal cell carcinoma (BCC), cystic lesions, and melanocytic lesions represent about 85% of all eyelid tumors.[2,3] The presence of a nodule or lesion on the eyelid that grows, bleeds, or ulcerates should be evaluated. This involves examination and sometimes a biopsy. Eyelid tumors include squamous cell carcinoma, sebaceous gland carcinoma, and malignant melanoma and BCC.[4] The present study was performed on 100 patients for evaluating the histopathology, overall incidence of benign and malignant eyelid tumors and its relation to different age groups and sex.

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MATERIALS AND METHODS

The present study was performed on 100 patients. Biopsy samples received in histopathology section of our institute from May 2008 to November 2010 were taken into study. General information of the patient including age and sex were taken. Gross examination and histological features were studied in detail. Eyelid biopsies were received in our laboratory in 10% formalin (as fixative). The initial gross examination includes size and color of the tissue, presence or absence of epidermis and hair, and distance to the nearest margin of discrete lesions. After examining the tissue, all surfaces except epidermis were inked before sectioning. If clinician had provided orientation for specific margin, inking with two or more colors was done. Shave biopsy or punch biopsies with greatest epidermal dimension <0.3 cm were submitted for processing without sectioning. Specimens with a greatest epidermal measurement of at least 0.4 cm were sectioned vertically through the epidermis along the long axis. Elliptical biopsies were oriented by sutures. Sections of an ellipse were taken at regular intervals of 2–3 mm. Gross tissues were cut in blocks and placed in 10% formalin. Fixation is usually complete at the end of 24 h and tissues are ready for processing. Total duration of processing is 13 h. Tissue blocks were kept in acetone bath, first two for 90 min, and then successive three for 60 min. Then, tissue blocks were kept in three bath of xylene, each for 1 h. Finally, kept in two bath of wax (temp. 52–62°C), each for 2 h. After paraffin processing, tissue blocks were cut on microtome knife, slide is prepared, and H and E stain was done. After drying, slides were mounted with DPX. Then, slides were examined under the microscope for histological diagnosis.

RESULTS

A total of 100 cases were studied. All histopathological specimens were adequate to make the final diagnosis.

Incidence of benign tumor was 56% while that of malignant tumors was 44%. Among benign tumors, melanocytic nevi and squamous papilloma were common while in malignant tumors, meibomian gland carcinoma was the most common tumor followed by BCC and squamous cell carcinoma [Table 1].

Epithelial tumors of the eyelid were the most common tumors (33%) while adnexal, melanocytic, and mesenchymal tumors were almost equal in the present study [Table 2].

Malignant epithelial tumors were common than benign tumors. Benign nevi were the most common melanocytic tumors. Meibomian gland carcinoma was the most common adnexal tumors. In mesenchymal origin, only benign tumors were found in which hemangiomas were the most common [Table 3].

Table 1: Incidence of benign and malignant tumors

Tumors	Cases (%)
Benign	
Nevus	21
Squamous papilloma	12
Hemangioma	8
Neurofibroma	7
Schwannoma	4
Lipoma	3
Syringoma	1
Total (benign)	56 (56)
Malignant	
Meibomian gland carcinoma	22
Basal cell carcinoma	12
Squamous cell carcinoma	9
Malignant melanoma	1
Total (malignant)	44 (44)
Total number of cases	100 (100)

Table 2: Distribution of tumors according to its origin

Tumors	Number of cases (%)
Epithelial origin	33 (33)
Adnexal origin	23 (23)
Melanocytic origin	22 (22)
Mesenchymal origin	22 (22)
Total	100

Benign tumors were more common in children, adolescent, and young adults. Malignant tumors were more common in elderly. Most common age group of benign tumors was 21–40 years while in malignant tumors, it was 61–80 years. In the age group of 21–40 years, total number of benign tumors found was 23, of which melanocytic nevi were the most common followed by squamous papilloma. Total numbers of malignant tumors found in the age group of 61–80 years were 22, of which meibomian gland carcinoma was the most common followed by BCC [Table 4].

Overall, the incidence of eyelid tumors in adults was 85%, and in children, it was 15%. In the present study, only benign tumors were found in children. In adults, benign and malignant tumors both were found. Incidence of malignant tumors was slightly higher than benign tumors in adults [Table 5].

Eyelid tumors were slightly more common in males as compared to females. Overall, the incidence of benign tumors was more common than malignant tumors in both sexes [Table 6].

Table 3: Occurrence of tumor according to its origin

Origin of tumor	Benign	Number of cases	Malignant	Number of cases	Total cases
Epithelial tumors	Squamous papilloma	12	Basal cell carcinoma	12	33
			Squamous cell carcinoma	9	
Adnexal tumors	Syringoma	1	Meibomian gland carcinoma	22	23
Melanocytic tumors	Nevi	21	Malignant melanoma	1	22
Mesenchymal tumors	Hemangioma	8	-	0	22
	Neurofibroma	7			
	Schwannoma	4			
	Lipoma	3			
Total cases		56		44	100

Table 4: Incidence of eyelid tumors according to age group

Tumors/age group	1–20	21–40	41–60	61–80	81–100
Papilloma	2	6	4	0	0
Basal cell carcinoma	0	1	5	6	0
Squamous cell carcinoma	0	2	6	1	0
Nevi	3	8	9	1	0
Melanoma	0	0	0	1	0
Syringoma	0	1	0	0	0
Meibomian gland carcinoma	0	0	6	14	2
Hemangioma	3	5	0	0	0
Neurofibroma	4	1	1	0	0
Schwannoma	1	2	1	0	0
lipoma	1	0	1	1	1
Total	14	26	33	24	3

DISCUSSION

The present study was performed on 100 patients. Results of the presents study were compared with the studies performed by other studies. Results of the present study were as follows:

The overall incidence of benign tumors was higher than malignant tumors. Among benign tumors, melanocytic nevi and squamous papilloma were common while in malignant tumors, meibomian gland carcinoma and BCC were the most common tumor. Epithelial tumors were the most common tumors in the present study. Benign tumors were more common in children, adolescent, and young adults. Malignant tumors were more common in elderly. Eyelid tumors were slightly more common in male as compared to females. However, the overall incidence of benign tumors was more common than malignant tumors in both sexes. Comparison with other studies:

A study conducted by the Department of Pathology, Universal College of Medical Science, Nepal[5] (37 cases), shows frequency of sebaceous gland carcinoma (40.5%), BCC (24.3%), SCC (27%), and melanoma (2.7%) while in the present study, the frequency of these tumors was 22%, 12%, 9%, and 1%, respectively. In both studies, most common malignant tumor was sebaceous gland carcinoma followed by BCC, SCC, and malignant melanoma. Results of both the studies were comparable.

Comparison of the incidences of malignant eyelid tumors - a study conducted by Ohtsuka *et al.*[6] (study of 38 cases) shows frequency of sebaceous gland carcinoma (28.9%), BCC (39.5%), and SCC (10.5%) while in the present study, the frequency of these tumors was 22%, 12%, 9%, and 1%, respectively. In comparison study, most common eyelid carcinoma are BCC followed by sebaceous gland carcinoma and SCC, while in the present study, sebaceous gland carcinoma is the most common followed by BCC and SCC.

Age incidence of eyelid cancers in Taiwan[7] (21 years review, retrospective study of 1166 cases) shows that age distribution of malignant eyelid tumors ranges from 48.5 to 76.7 years, while in the present study, it ranges from 41 to 80 years.

A study was conducted by the Department of Ophthalmology, College of Medicine, Korea University. Ansan Hospital[8] (a study of 95 cases) shows that the mean age of benign tumor was 30–42 years while in the present study, age distribution of benign papilloma is 21–40 years and benign nevi is 31–50 years.

A study by Lee *et al.* on eyelid cancers in Singapore from 1968 to 1995[9] on sex distribution of eyelid tumors show that tumor occurrence in males (49.8%) and females (50.2%) while in the present study, it was 52% and 48%, respectively. Sex ratio in the present study and comparison study was almost near to equal.

Results of the comparison studies were as follows:

The most common malignant tumor of the eyelid was sebaceous gland carcinoma and BCC. Malignant tumors were more common in elderly while benign tumors were more common in young adults. Sex distribution of benign

Table 5: Distribution of benign and malignant tumors in children and in adults

Benign tumors	Pediatric age (<18 years)	Adults (>18 years)	Malignant tumors	Pediatric age (<18 years)	Adults (>18 years)
	Number of cases			Number of cases	
Neurofibroma	5	2	Meibomian gland carcinoma	0	22
Hemangioma	3	5	BCC	0	12
Nevi	3	18	Squamous cell carcinoma	0	9
Papilloma	2	10	Melanoma	0	1
Schwannoma	1	3			
Lipoma	1	2			
Syringoma	0	1			
Total	15	41		0	44

BBC: Basal cell carcinoma

Table 6: Incidence of benign versus malignant tumors in both sexes

Benign	Male	Females	Malignant	Male	Female
papilloma	7	5	BCC	7	5
Nevi	8	13	Squamous cell carcinoma	8	1
Syringoma	0	1	Meibomian gland carcinoma	8	14
Hemangioma	4	4	Malignant melanoma	0	1
Neurofibroma	5	2			
Schwannoma	3	1			
lipoma	2	1			
Total	29	27		23	21
Total (overall)	52 (29+23)	48 (27+21)			

BCC: Basal cell carcinoma

and malignant tumors was almost equal. Results of the present study were comparable with other studies.

CONCLUSION

The present study was concluded with the following results: A total of 56 cases of benign tumors were found. Incidence is 56%, seven types of benign tumors were found: Melanocytic nevi (21%), papilloma (12%), hemangioma (8%), neurofibroma (7%), schwannoma (4%), lipoma (2.70%), and syringoma (1%). A total of 44 cases of malignant tumors were found. Incidence is 44%, four types of malignant tumors were found: Meibomian gland carcinoma (22%), BCC (12%), squamous cell carcinoma (9%), and malignant melanoma (1%). Incidence of meibomian gland carcinoma was highest in the present study. However, overall, the incidence of benign tumors was more than malignant tumors. Benign tumors were more common in adolescent and young adults. Mean age of benign tumors was 33.83 years. Malignant tumors were more common in elderly. Mean age of malignant tumors was 61.40 years. Overall, sex distribution of benign and malignant tumors is equal in both the sexes.

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Original Article

Evaluation of Quality of Life in Nasopharyngeal Carcinoma based on EORTC QLQ-H and N35 and Karnofsky Scale in Adam Malik General Hospital Medan

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Abstract

Introduction: Nasopharyngeal carcinoma (NPC) is a malignant epithelial cell that lines the nasopharyngeal surface and is a neck head malignancy that has received much attention due to the relatively high mortality rate. Evaluating the quality of life for patients with malignancies is important as an "end-point" for treatment and an indicator of patient monitors.

Method: This study is an analytical study with cross-sectional research design by analyzing the EORTC QLQ-H and N35 and Karnofsky Scale on 60 NPC patients.

Results: Most NPC patients were male, most in Stages III and IV. The most histopathological type is non crystallizing SCC. Based on EORTC QLQ-H and N35, the most complaints of patients with NPC were found to be weight loss and the use of painkillers Karnofsky scores of NPC patients who were assessed as having a mean of 70.33.

Conclusion: There is a significant correlation between EORTC QLQ - H and N35 with Karnofsky scores ($r = -0.612$; $P = 0.000$). The greater the Karnofsky value, the smaller the value of EORTC QLQ - H and N35 means that the quality of life of the patient is getting better, and vice versa

Key words: EORTC QLQ-H and N35, Karnofsky scale quality of life, Nasopharyngeal carcinoma

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an epithelial cell malignancy on the nasopharyngeal surface and is one of the neck head malignancies that have received much attention due to high mortality rate.[1] The highest incidence in the world is in the Southeast China Province, which is 40–50 cases of NPC between 100,000 population.[2] In RSUP H. Adam Malik Medan in 1998–2000, there were 130 patients with NPC from 1370 new patients on head and neck oncology.[3]

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Evaluation of quality of life in patients with malignancy is important in the field of oncology but depends on the type of malignancy and stage, because some types of malignancy do not provide symptoms until the advanced stage. Quality of life has been introduced as an "end-point" for treatment and is an early indicator of disease progression that can help monitor patients.[4]

According to Taher, with research on 87 head and neck malignancy patients with histopathology of squamous cell carcinoma, treatment modalities have a significant negative affect on the quality of life. Tumor location, clinical stage, treatment modality, sex, age, and smoking habits had a statistically significant impact on quality of life at the end of the treatment period. It has the worst impact on taste and smell sensation, weight loss, dry mouth, thick retention of saliva, pain, loss of appetite, nausea and vomiting, and fatigue.[5]

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EORTC QLQ-H and N35 have a symptom scale both in multiple and single items, and there are, still, no data that adequately support whether the use of EORTC QLQ-H and N35 alone is valid and reliable enough to be used in NPC patients who get various types of treatment modalities; thus, the researchers interested in analyzing the correlation between EORTC QLQ-H and N35 parameters and Karnofsky Scale and the suitability of the scores between the two questionnaires in assessing the quality of life for NPC patients to determine whether overall quality of life of NPC patients can be assessed with far better results when using multidimensional parameters with EORTC QLQ-H and N35 combined with Karnofsky Scale.

METHOD

This study is an analytical study with a cross-sectional research design. The study was conducted at H. Adam Malik General Hospital in Medan. It was conducted from August 2017 to March 2018. The population of this study were all NPC patients who were outpatient or hospitalized at H. Adam Malik Hospital Medan. The samples of this study were NPC patients who were just going to undergo therapy, NPC patients on therapy, and NPC patients who had undergone therapy at H. Adam Malik General Hospital Medan. Inclusion criteria: NPC patients with complete medical records containing all data needed and willing to fill out the EORTC QLQ-H and N35 and Karnofsky Scale questionnaires. Exclusion criteria: The questionnaire was not filled in completely and uncooperative samples and had severe comorbidities that were not associated with NPC.

The data obtained were analyzed statistically to analyze the EORTC QLQ-H and N35 and Karnofsky Scale correlations in assessing the quality of life of NPC patients in H. Adam Malik Hospital Medan. Data collected and analyzed with a computer program and present ontable.

RESULTS

This study was conducted on 60 NPC patients who came to RSUP H. Adam Malik Medan from July to December 2017. The subjects were all NPC patients who had not, were or had undergone chemoradiotherapy who met the inclusion and exclusion criteria of the study.

NPC patients increased from age groups of the third decade and peaked in fifth decade. The mean age is 43.02 ± 13.385 years (mean ± SB). In this study, the youngest NPC patient was 18 years, and the oldest was 73 years.

The majority of NPC patients were male (80%), with 20% being female. In this study, the highest number of patients was found in Stage IVB as many as 29 people (48.3%) followed by Stage III with 13 people (21.6%). The histopathological type in 46 patients (76.7%) found to be nonkeratinizing SCC followed by undifferentiated types with 11 patients (18.3%) and SCC keratinizing types with 3 patients (5.0%).

The assessment of the quality of life of NPC patients was carried out in patients undergoing chemoradiotherapy totaling 35 patients (58.3%), the remaining 15 were patients who had not undergone chemoradiotherapy (25%) and in patients who had undergone chemoradiotherapy as many as 10 patients (16.7%).

Assessment of the quality of life-based on EORTC QLQ-H and N35 with various types of symptoms as noted above, the most common problem of NPC patients were weight loss and painkillers obtained Karnofsky scores in NPC patients with a mean of 70.33 ± 14.258 (mean ± SB).

DISCUSSION

In Indonesia, NPC is the 4th most malignancy after breast cancer, cervical cancer, and lung cancer[1]. Based on official data from the Ministry of Health, the prevalence of nasopharyngeal cancer patients in Indonesia is 4.7 people per 100,000 population a year.[6] In RSUP H. Adam Malik Medan in 1998–2000, there were 130 patients with NPC from 1370 new patients on head and neck oncology.[3]

In this study, we found NPC patients increased from the age group in the third decade and peaked in the fifth decade. The average age is 43.02 ± 13.385 years (mean ± SB). The highest number of patients with NPC in the age group ≥50 years is 21 (35.0%) and at least in the age group ≤20 years is 3 (5.0%), with the youngest age is 18 years, and the oldest is 73 years.

Nearly 60% of NPC patients aged between 25 and 60 years.[7] In endemic areas, the incidence increases since the age of 20 years and reaches a peak in the fourth decade and decade five.[8]

Research at H. Adam Malik General Hospital in Medan with a series of cases by Lutan received the highest incidence at 40–49 years old by 40% from 130 cases,[3] another Puspita study (2011) had the highest incidence in the age group 51–60 years as much as 26.5% of 335 cases and the highest frequency of histopathological type was squamous cell without creatinization 46.6%.[9]

In this study, we found that most NPC patients were men 48 (80%), and the rest were women 12 (20%), the results of this study were not too different from the results of

previous studies in Yogyakarta and at RSCM Jakarta with a ratio of 4, 5: 1, and 4.7: 1.[10]

From a worldwide survey conducted in 2012, there were 87,000 new cases of NPC appearing annually. 61,000 new cases were found in men and 26,000 new cases in women.[11]

Men who suffer more from NPC compared to women are reported in almost all studies; this is thought to have something to do with living habits and work that causes men to come in contact with carcinogens that cause NPC. Steam exposure, dust smoke, and chemical gas in the workplace increase the risk of KNF 2–6 times, while exposure to formaldehyde in the workplace increases risk 2–4 times. In addition, the dominant hormone testosterone in men is suspected of causing a decrease in the immune response and surveillance of tumors so that men are more susceptible to EBV infection and cancer.[12]

In this study, the most patients with NPC were found in Stages III and IV. In Indonesia, when diagnosed the patient is usually at an advanced stage, only 10% of cases are diagnosed at an early stage.[13]

Clinical diagnosis of KNF is difficult because the location of the nasopharynx is hidden, so most diseases have developed into advanced stages where the size and lymph nodes are large enough to be found.[14] Patients who come for treatment at RSUD Dr. Saiful Anwar were found at 0.81% (Stage I), 4.88% (Stage II), 38.21% (Stage III), and 56.10% in Stage IV.[15]

In our study, the most common histopathological type in NPC patients was non-crinizing SCC (76.7%) followed by undifferentiated type (18.3%) and keratinizing SCC type (5.0%). Different from the research conducted by Kurniawati *et al*., it was reported that the type of undifferentiated NPC histopathology was 70.8%, non-creatinizing type was 29.2%, and keratinizing type was 0%.[16]

In some studies found that the WHO Type 3 is the most common type in Southeast Asia.[17] In the WHO Type 2 and 3 KNF, high Epstein Barr virus (VEB) titers were encountered, while Type 1 did not have a relationship with VEB titers. The WHO Type 1 KNF is predominantly found in Caucasian ethnicities as in Europe.[18] From the results of these studies, there was a difference in the dominance of histopathological types in each study in different locations. Differences in geographical and racial/ethnic distribution on KNF in the world suggest that environmental and genetic factors may play a role in this difference.[7]

In this study, an assessment of the quality of life of NPC patients was carried out in patients undergoing chemoradiotherapy (58.3%), the remaining 25% in patients who had not undergone chemoradiotherapy and in patients who had undergone chemoradiotherapy as much as 16.7%.

In Indonesia so far one study has been reported on the quality of life in HNC sufferers (before, moderate, or after therapy), and two studies on the quality of life of NPC patients. Research using EORTC QLQ-H and N35 in NPC patients before therapy showed a poor quality of life (64.7%). However, the assessment of the quality of life of patients after therapy has never been reported.[15] The quality of life of NPC patients is not only based on tumor stage or size but also based on chemotherapy treatment and radiotherapy.

From the assessment of the quality of life-based on EORTC QLQ-H and N35 with various types of symptoms in this study, the complaints of the most NPC patients were found to be weight loss and use of painkillers. In addition, in this study obtained Karnofsky scores in NPC patients who assessed their quality of life with a mean of 70.33 ± 14.258 (mean ± SB). In this study, it was found that many patients with Stage IV who had spread to the cranii base which caused the most common symptoms were headache, so that explain the use of painkillers.

The assessment of the quality of life of cancer patients is considered necessary because with the assessment of the quality of life of these patients can be used as a parameter to assess the quality of cancer therapy in patients. To measure the quality of life should be multidimensional involving physical, social, and emotional aspects such as EORTC QLQ H and N35, which is a questionnaire specifically intended for patients with head and neck malignancies.[19]

EORTC QLQ H and N35 is a specific module intended for head-neck cancer patients. Consists of 35 questions, which can be grouped into seven multi-item scales and 11 single item scales. The interpretation of the scale produced is 0–100 where the function scale 100 explains that the better the quality of life. While the scale of the symptoms, the higher the number obtained, the more perceived burden.[20]

It was reported that in patients with head and neck malignancies, the more age and tumor stage increases, the lower the physical status/Karnofsky Performance Scale.[21]

In this study, the subjects who had not undergone therapy were as many as 15 people, it appears that only 10 components of the EORTC QLQ H and N 35 assessment have a significant correlation with the Karnovsky score and all with a negative direction. The assessment component of EORTC QLQ H and N 35 which has a strong correlation

with Karnofsky score is pain, troubles with social eating, opening mouth, and dry mouth, according to research. Patients with nasopharyngeal tumors have the worst functional and social values compared the other group, had the highest pain score and dry mouth complaints before therapy.[22]

In this study, there were 15 patients who had not undergone chemotherapy; there were 1 Stage III patient, 2 Stage IVa patients, and as many as 12 people with Stage IVb. The Karnofsky score correlation with each component of the EORTC variable can only be performed on patients/subjects with Stage IVb, symptoms, opening mouth pain, dry mouth, weight loss, and trouble with social eating. According to research stated that the appearance of symptoms and the severity of the stage of the disease and its associated Karnofsky scale and thick salivary disorders, use of painkillers, weight loss, especially found in pharyngeal tumors.[23,24]

The difficulty of protecting important structures around the nasopharynx causes toxicity due to radiochemotherapy is difficult to avoid, especially due to conventional two-dimensional radiation therapy. The main toxicity of radiotherapy is xerostomia, trismus, dysphagia, and hearing loss. This toxicity will limit the physical function of the patient and trigger the development of psychological problems, such as anxiety, fear, depression, and depression which will affect the quality of life of patients. The quality of life is also significantly affected by the time of evaluation after therapy, age, and socioeconomic status of the patient.[15]

In this study, we found a significant correlation (P= 0.000, P <0.05) between EORTC QLQ-H and N35 with Karnofsky scores, with a correlation relationship that was inversely proportional (r = −0.612). This means that the greater the value of Karnofsky scores, the smaller the value of EORTC QLQ-H and N35 (the quality of life of patients is getting better), and vice versa.

There is a match between Karnofsky scale score and EORTC QLQ-H and N35 score in assessing the quality of life of patients with NPC (Awad, *et al*., 2008) where there is a significant correlation between the three parameters. The lower the EORTC QLQ-H and N35 score, the better the quality of life. EORTC QLQ-H and N35 scores can also estimate Karnofsky PS scores, with the standard value of EORTC QLQ-H and N35 score errors smaller than EORTC QLQ-C30 scores, so EORTC QLQ-H and N35 are more sensitive to estimating them.[25]

Based on this, it can be interpreted that the higher the score of the Karnofsky score, the better the quality of life, the lower the EORTC QLQ H and N35 score, the better the quality of life.

Thus, the hypothesis of this study is that there is a correlation between the assessment of the quality of life of KNF sufferers using EORTC QLQ-H and N35 and Karnofsky scores revealed.

CONCLUSION

In this study, there was an increase in the number of NPC patients from the age of the third decade, with a mean age of 43.02 ± 13.385 years (mean ± SB). The youngest age is 18 years and the oldest is 73 years. In this study, the most NPC patients were men. In this study, the most patients with NPC were found in Stage III and IV. In the study, the highest histopathological type was found to be non-crinizing SCC (76.7%).

In this study, an assessment of the quality of life of NPC patients was performed in patients who were undergoing chemoradiotherapy as much as 58.3%, in patients who had not undergone chemoradiotherapy as much as 25% and in patients who had undergone chemoradiotherapy as much as 16.7%. From the assessment of the quality of life-based on EORTC QLQ-H and N35 with various types of symptom in this study, the complaints of most NPC patients were found to be weight loss and painkillers. In this study, the score of Karnofsky scores of NPC patients was found to be an average of 70.33 ± 14.258 (mean ± SB).

There is a significant correlation between EORTC QLQ-H and N35 with Karnofsky scores (r = −0.612; P = 0.000). The greater the value of Karnofsky scores, the smaller the value of EORTC QLQ-H and N35 means that the quality of life of the patient is getting better, and vice versa.

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Original Article

Isolation of Methicillin-resistant *Staphylococcus aureus* from Neonatal Sepsis at a Tertiary Care Hospital

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Abstract

Introduction: Septicemia is the significant cause of morbidity and mortality in the neonates and is responsible for 30-50% of total neonatal deaths .Each year in developing countries. It is estimated that 20% of all neonates develop sepsis and approximately 1% die of sepsis related causes.In India, according to National Perinatal Database the incidence of neonatal septicemia has been reported to be 30/1000 live births. The emergence of methicillin resistant Staphylococcus aureus (MRSA) in neonatal patients is increasing. Early diagnosis and appropriate therapy of septicemia is of utmost importance to prevent morbidity and mortality.

Aim and Study: It was to find out the bacteriological profile in neonatal sepsis and study their antimicrobial susceptibility pattern including detection of MRSA.

Methods: This study was conducted for a period of one year in the department of microbiology in a tertiary care hospital. A total of 283 blood samples were collected using sterile precautions They were processed following standard laboratory protocol. Antibiogram was done using appropriate antibiotics by Kirby-Bauer disc diffusion method. Isolated of Staphylococcus aureus were tested for methicillin resistance.

Results : Blood from 283 neonates with the clinical signs and symptoms of sepsis were collected and samples were processed. Out of which 96 (33.92%) were culture positive.Total 53 (55.2%) Staphylococcus aureus were isolated out of which 27 (50.94%) were MRSA (Methicliin Resistant Staphylococcus aureus).Acinetobacter spp.was isolated in 15 (15.62%) cases.Klebsiella spp. was isolated in 13 (13.54%) cases. Psedomonas spp. was isolated in 3(3.12%) case . Antibiotic sensitivity test of MRSA was done and all MRSA isolates were sensitive to Vancomycin.

Conclusion: Multidrug resistance among the isolates was common. Early diagnosis and institution of specific antibiotics after studying the sensitivity pattern will help in reducing neonatal morbidity and mortality and prevent emergence of drug resistant strains. An effective infection-control programme, regular antibiotic susceptibility surveillance ,evaluation, and the enforcement and periodic review of the antibiotic policy of the hospital as well as the encouragement of rational antibiotic use will reduce the rates of development of bacterial resistance.

Key words: Septicemia, Neonate, Methicillin, Vancomycin, Drug resistance

INTRODUCTION

In the developing world, septicemia in neonates is one of the major causes of morbidity and mortality among the newborns. It is defined as "a clinical syndrome which is characterized by systemic signs and symptoms and bacteremia during the 1st month of life." It is "early-onset" disease, if it presents during the first 5–7 days of life and it is "late onset" if it occurs after the 1st week of life.[1]

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Sepsis is the most common cause of neonatal mortality and each year in developing countries it is responsible for 30–50% of total neonatal deaths. It is estimated that 20% of all neonates develop sepsis and approximately 1% die of sepsis-related causes. National Neonatal-Perinatal Database

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from India has reported an incidence of the neonatal sepsis of 0.1–4.5% from 18 hospitals across India and the incidence of blood culture-proven sepsis was reported as 8.5/1000 live births.[2]

The factors which are associated with sepsis in newborns include low birth weight, fetal distress, a low Apgar score, the requirement of mechanical ventilation, umbilical catheterization, and a history of preeclampsia in the mothers.[1]

The microorganisms most commonly associated with early-onset septicemia include Group B *Streptococcus, Escherichia coli,* coagulase-negative *Staphylococcus* species (CONS), *Haemophilus influenza,* and *Listeria monocytogenes* and late-onset septicemia is caused by CONS, *Staphylococcus aureus, E. coli, Klebsiella spp., Pseudomonas spp., Enterobacter spp., Candida spp.,* GBS, *Serratia spp., Acinetobacter spp.,* and anaerobes. The recent trends show an increase in infections due to CONS. The knowledge of bacteriological profile and its antibiotic sensitivity patterns is of immense help in saving lives of neonates with septicemia.[4]

An early treatment and the appropriate and the rational use of antibiotics can minimize the risk of severe morbidity and mortality in neonatal sepsis, and reduce the emergence of multidrug-resistant organisms. For the success of an early empiric treatment, a periodic review of the cases to assess any changing trends in the infecting organisms and their antimicrobial susceptibility is important.

The emergence of methicillin-resistant *S. aureus* (MRSA) in neonatal patients is increasing. The aim of this study was to find out the bacteriological profile in neonatal sepsis and study their antimicrobial susceptibility pattern including detection of MRSA.

MATERIALS AND METHODS

This study was conducted for a period of 1 year in the department of microbiology in a tertiary care hospital.

Inclusion Criteria

Neonates clinically suspected of having sepsis, temperature >99°F or <95°F, respiratory rate>60/min, abnormal cry, refusal of feed, drowsy or unconscious, septic focus on skin or umbilicus, diarrhea, and seizures were included in the study [Chart 1].

Exclusion Criteria

Neonates already on antibiotics and with diagnosis of intrauterine infection and congenital anomalies were excluded from the study.

A total of 283 neonates (0–28 days) with the clinical signs and symptoms of sepsis were included in this study. The neonates with congenital malformations or dysmorphic features were excluded from the study. The neonatal septicemia was categorized according to its time of onset as early-onset sepsis (0–7 days) and late-onset sepsis (8–28 days). An informed consent was taken from the parents of the neonates before the performance of this study. All the blood cultures were collected from the peripheral veins by following proper aseptic precautions before any antibiotic therapy was started with. Blood specimens were collected aseptically into BACTEC blood culture bottles after cleaning proposed venipuncture sites with 70% alcohol, then povidone iodine, and finally, 70% alcohol to remove the iodine at the end of venipuncture. Approximately, 2–3 ml of blood was inoculated into BACTEC blood culture bottles. The inoculated bottles were transported immediately to the department of microbiology and they were incubated in BACTEC blood culture system. Gram stain and subcultures using MacConkey and blood agar plates were done from culture bottles where growths were indicated, other specimens were inoculated on MacConkey agar and blood agar and incubated at 35–37°C for 18–24 h. The colonies which were isolated were identified on the basis of their colony morphology their Gram staining patterns and their standard biochemical tests. The antibiotic sensitivity patterns of the isolates were studied using the Kirby–Bauer disc diffusion technique. Detection of MRSA isolates was done using 1 μg oxacillin disc on Mueller-Hinton agar supplemented with an additional 5% NaCl and cefoxitin disc (30 ug) diffusion test, and results were interpreted according to the Clinical and Laboratory Standards Institute guidelines.[5]

RESULTS

This study was conducted for a period of 1 year in the department of microbiology in a tertiary care hospital. Blood from 283 neonates was collected and samples were processed, of which 96 (33.92%) were culture positive.

A total of 53 (55.2%) *S. aureus* were isolated, of which 27 (50.94%) were MRSA. *Acinetobacter spp.* was isolated in 15 (15.62%) cases. *Klebsiella spp.* was isolated in 13 (13.54%) cases. *Pseudomonas spp.* was isolated in 3 (3.12%) cases. Other organisms were in 12 (12.5%) cases. Antibiotic sensitivity test of MRSA was done and all MRSA isolates were sensitive to vancomycin [Chart 2].

DISCUSSION

In the present study, blood from 283 neonates was collected and samples were processed, of which 96 (33.92%) were

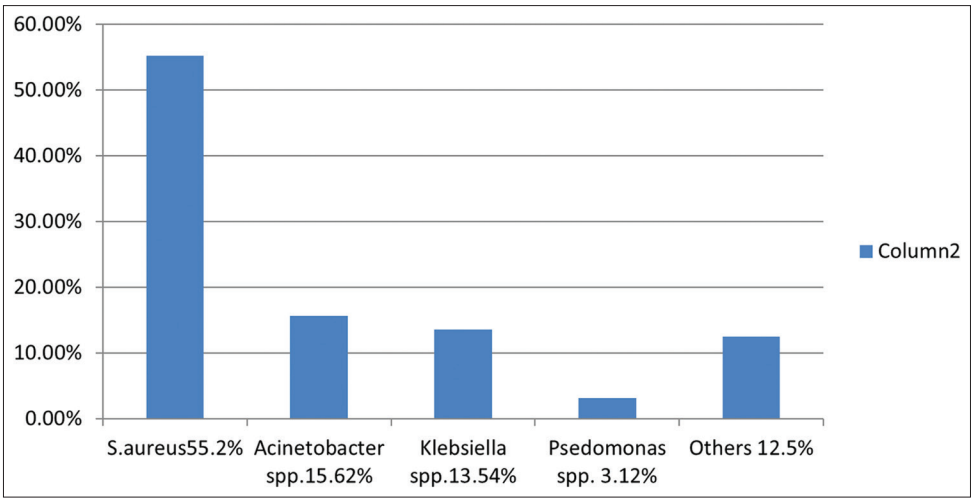

Chart 1: Organisms isolated from positive cultures of neonatal sepsis

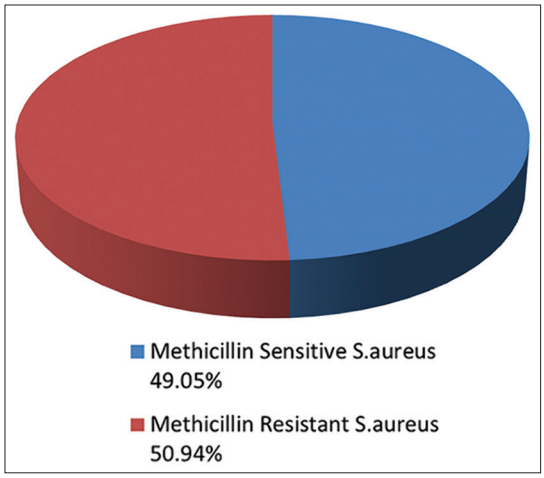

Chart 2: Methicillin sensitivity of *Staphylococcus aureus*

culture positive. A total of 53 (55.2%) *S. aureus* were isolated, of which 27 (50.94%) were MRSA

In the study done by Poonam Sharma *et al.*, a total of 131 organisms were isolated from the 311 blood cultures samples of neonates. Of these positive cultures, *S. aureus* were 68 (51.9%). Of these 68 *S. aureus* isolates, 39 (57.35%) were MRSA.[1]

In the study done by Chelliah *et al.*, of the 182 cases, 110 (60.4%) were culture positive. 30 (27%) were *S. aureus,* of which 17 (56.6%) of *S. aureus* were found to be MRSA.[2]

In a study done by Muley *et al.*, out of 180 blood samples, septicemia was confirmed by culture in 26.6% (48 of 180) of cases. Out of which *S. aureu*s was accounting for and 22.9% cases. 18.1% of *S. aureus* isolates were found to be methicillin resistant.[3]

In a study done by Thakur *et al.*, of a total of 450 neonates investigated with blood culture, 188 (42%) were found to be positive for neonatal septicemia. of 188 (42%) positive blood cultures, the Gram-positive bacteria and Gram-negative bacteria accounted for 60% and 40%, respectively. Among Gram-positive organisms, 66% isolates were *S. aureus,* of this methicillin resistance was detected in 29 (41%) of *S. aureus.*[4]

In a study done by Macharashvili *et al.*, 40% of *S. aureus* isolates were MRSA.[6]

In the study done by Ramesh Agrawal *et al.*, methicillin resistance prevailed in 61% (85/140) of coagulase-negative staphylococci and 38% (43/114) of *S. aureus* isolates.[7]

In a study done by Kung *et al.*, MRSA was detected in 12.8% of cases of the neonatal sepsis.[8]

In the study done by Pai, methicillin resistance was documented in 69 (29.1%) of 237 isolates.[10]

In the study done by Tiwari *et al.* among 783 isolates of *S. aureus*, 301 (38.44%) isolates were methicillin-resistant.[11]

Multidrug resistance among the isolates was common. Early diagnosis and institution of specific antibiotics after studying the sensitivity pattern will help in reducing neonatal morbidity and mortality and prevent emergence of drug-resistant strains.

In the present study, antibiotic sensitivity test of MRSA was done and all MRSA isolates were sensitive to vancomycin.

In the study done by Sharma *et al.*, most effective antibiotic against the MRSA isolates was vancomycin and sensitivity to vancomycin was 100%.[1]

In the study done by Chelliah *et al.*, 17 (56.6 %) of *S. aureus* were found to be MRSA and they were 100% sensitive to vancomycin.[2]

In a study done by Muley *et al.*, 18.1% of *S. aureus* isolates were found to be methicillin resistant. Vancomycin remains the drug of choice for MRSA strains.[3]

In a study done by Thakur *et al.*, methicillin resistance was detected in 29 (41%) of *S. aureus.* There were 30 (40%) MDR isolates among the total of 75 isolates of *S. aureus.* All the isolates were sensitive to vancomycin.[4]

In a study done by Nino *et al.*, 40% of *S. aureus* isolates were MRSA and all were susceptible to vancomycin.[6]

In the study done by Roy *et al.*, all *S. aureus* isolates were sensitive to vancomycin.[9]

In the study done by Tiwari *et al.* among 783 isolates of *S. aureus*, 301 (38.44%) isolates were methicillin-resistant.[11]

Therefore, regular surveillance of infections including antimicrobial susceptibility pattern of MRSA and formulation of a definite antibiotic policy may be helpful in reducing the burden of MRSA infections. Vancomycin should be used when the patient does not respond to the first-line treatment or the combination of drugs.

CONCLUSION

Neonatal sepsis is an important cause of neonatal mortality and it depends on the age of onset of sepsis and on the etiologic agent and their resistant pattern. Implementation of infection control measures, restricting the use of broad-spectrum antibiotics, rotation of antibiotics, and rationalizing the use of antibiotics can decrease antibiotic resistance. Early diagnosis and specific treatment can reduce neonatal mortality and morbidity. Therefore, regular surveillance of infections including antimicrobial susceptibility pattern of MRSA and formulation of a definite antibiotic policy may be helpful in reducing the burden of MRSA infections. Vancomycin should be used when the patient does not respond to the first-line treatment or the combination of drugs.

Multidrug resistance among the isolates was common. Early diagnosis and institution of specific antibiotics after studying the sensitivity pattern will help in reducing neonatal morbidity and mortality and prevent emergence of drug-resistant strains. An effective infection control programme, regular antibiotic susceptibility surveillance, evaluation, and the enforcement and periodic review of the antibiotic policy of the hospital as well as the encouragement of rational antibiotic use will reduce the rates of the development of bacterial resistance.

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Original Article

Fine-needle Aspiration Cytology in Palpable as Well as in Non-palpable Breast Lesions: A Study of 430 Cases

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Abstract

Background: Fine-needle aspiration cytology (FNAC) is an established, highly accurate, and cost-effective method for diagnosing lesions in different organs including the breast. The method is minimally invasive without unwanted side effects. At present, accurate diagnosis of breast lesions depends on a triple assessment approach that is combined clinical, radiological, and pathological diagnosis. FNAC is widely adopted for pathological diagnosis of different types of the breast lesions. In developing countries, like India, malignant causes as well as non-malignant causes are the most common causes of breast lump. FNAC proves to be a valuable tool in diagnosing these cases.

Aims: This study intended to look the frequencies and various cytomorphological presentations of different lesions on FNAC of breast lump.

Materials and Methods: In a study period of January 2015–December 2017, in the Pathology Department, GMERS Medical College, Ahmedabad, 430 patients of breast lesions for FNAC came. Those were subjected to cytological evaluation with hematoxylin and eosin, Giemsa, Papanicolaou, and Ziehl–Neelsen stained smears. We assessed the age of the patients, lesion size, site, type of lesion, and axillary lymph node metastasis in case of malignancies. In addition, the ultrasonography/mammography of these patients with the clinical presentation was also studied.

Results: Age ranges from 13 to 100 years with a mean age of 38 years. Among the lesions, 31.86% fibroadenoma, 23.02% malignant lesions, 11.81% fibrocystic changes, and 20.23% inflammatory lesions were identified. Mean lesion size was 3.37 ± 2.08 cm. 12 (12.12%) of malignant lesion cases showed metastasis in axillary lymph nodes.

Conclusion: FNAC serves as a safe, rapid, economical, requiring minimal instrumentation, and highly sensitive tool for the diagnosis of different kind of the breast lesions and ductal carcinoma. The cytomorphological examination of these lesions before operation or treatment serves as an important diagnostic modality. The sensitivity can be further increased by complementing with radiological and clinical findings.

Key words: Breast, Cytology, Ductal carcinoma of breast, Fine-needle aspiration cytology, Triple assessment

INTRODUCTION

Breast pathology is one of the most common pathologies encountered in routine practice. Not only the malignant lesions pose a major public health problem but also the benign lesions can contribute to the morbidity and their masquerade as malignancy can cause significant plight to the patients. The high incidence of breast malignancy, its relatively easy detection at an early stage, and effective treatment in the form of conservative surgery and chemotherapy had prompted a worldwide initiation of triple assessment including a clinical (palpation), radiologic (ultrasonography or mammography), and cytological (fine-needle aspiration cytology [FNAC]) assessment.[1,2]

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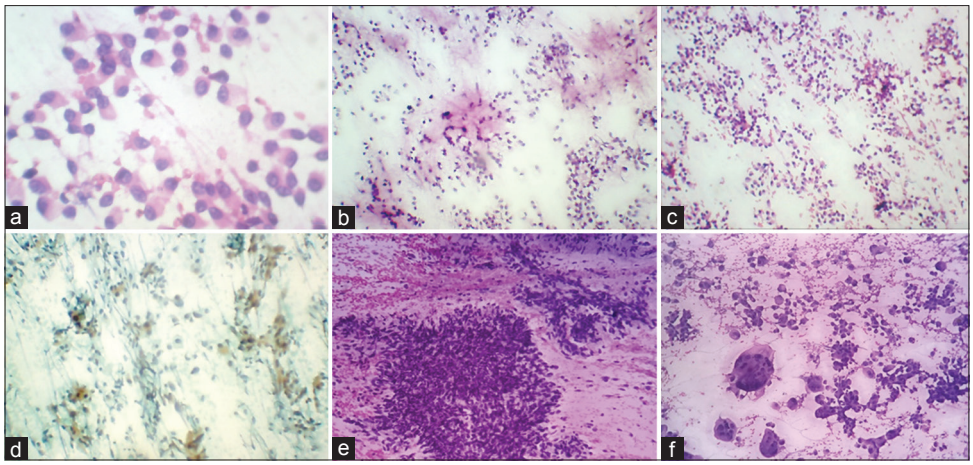

Figure 1: (a) Neuroendocrine type of breast carcinoma. (H and E × 400), (b) mucinous carcinoma of breast (H and E × 100), (c) ductal carcinoma of breast (H and E × 100), (d) metaplastic carcinoma of breast (PAP × 100), (e) sarcoma of breast (PAP × 100), (f) ductal carcinoma with osteoclastic-type giant cells (H and E × 100)

FNAC is a simple, quick, and reliable as well as cheap technique for obtaining diagnostic material. True fine needles for breast aspirations were first introduced in the beginning of 1960s by Franzén and Zajicek at Karolinska Hospital in Stockholm.[3,4] Being an oncologist, Franzen introduced standard May-Grunwald-Giemsa (MGG) stains on air-dried smears to allow for rapid interpretation.

The artillery of FNAC is fraught with its (1) rapid diagnosis, (2) pre-operative planning, (3) high acceptance, (4) high sensitivity and specificity, (5) ability to sample multiple areas at a single go, (6) sampling of metastatic as well as the primary site, (7) cost-effectiveness, (8) performance of ancillary techniques, and (9) a rapid psychological relief to the patient following a negative diagnosis. In addition, therapeutic aspiration is also possible in case of a cyst. FNAC can be employed in both palpable and non-palpable lesions of the breast, and it is a relatively safe procedure with a low rate of procedure-related complications.

The purpose of our study was to evaluate the accuracy of FNAC in diagnosing malignancy or other non-malignant causes and studying the frequency and distribution of various types of the breast lesions on FNAC in patients with breast lesions in peripheral areas of Ahmedabad.

MATERIALS AND METHODS

A total of 430 patients with palpable or suspected breast lump were aspirated for cytological evaluation in a study period of January 2015–December 2017 at GMERS Medical College, Ahmedabad. Appropriate approval of the institutional ethical committee was obtained for the same. Informed written consent from each patient was also obtained in local (Gujarati) language. The subjects concerned included all the female/male patients which were referred to the Department of Pathology, GMERS Medical College, Sola, Ahmedabad, from attached Sola civil hospital for FNAC of breast mass. Physical examination of breast mass by palpation was done. Palpable axillary lymph node was also selected for FNAC. Aspirations were performed using 22G/23G needles and disposable 10 ml/5 ml plastic syringe. Aspirated material was spread on 4–5 slides. The smears were fixed with methyl alcohol and stained with hematoxylin and eosin/Papanicolaou stain; one air-dried smear was stained with MGG stain. In cases where aspirated material appeared, necrotic one smear was stained with Z-N technique and an additional slide was kept unstained for any further required stain. Radiological findings of patients also studied. Data were recorded regarding the age of the patient, site of involvement, size of the lesion, cytological diagnosis, and presence of metastasis in case of malignancies.

Table 1: Reporting categories for FNAC breast lesions[5,6]

C1	Unsatisfactory
C2	Benign
C3	Atypia probably benign
C4	Suspicious of malignancy
C5	Malignant

FNAC: Fine-needle aspiration cytology

Cytology findings were grouped into five categories: Unsatisfactory, benign, atypia probably benign, suspicious, and malignant. Specimen adequacy was defined by our cytopathologists, based on the Bethesda conference on breast cytology guidelines, Table 1.[5,6] An adequate benign specimen required at least six well-visualized cell groups. A hypocellular or sparsely cellular specimen was considered unsatisfactory or non-diagnostic. A specimen was considered suspicious if the cellular findings were suggestive but not diagnostic of malignancy; additional

tissue biopsy was recommended in these cases. A malignant diagnosis was made when sufficient well-preserved malignant cells were identified. Typing of benign diseases as well as malignancy was also done.

Table 2: Radiological evaluation of breast lump

USG/Mammography result	Cytology result			
	Malignant	Suspicious	Benign	Total
Overall				
Malignant	96	00	00	96
Benign	03	09	322	334
Total	99	09	322	430
≤40 years				
Malignant	14	00	00	14
Benign	03	04	259	276
Total	17	04	259	270
>40 years				
Malignant	82	00	00	82
Benign	00	05	73	78
Total	82	05	73	160

USG: Ultrasonography

Table 3: The cytological categories of various palpable breast lesions

Cytological categories	*n* (%)
C1 unsatisfactory	12 (2.79)
C2 benign	300 (69.76)
C3 atypia probably benign	10 (2.32)
C4 suspicious of malignancy	9 (2.09)
C5 malignant	99 (23.02)

RESULTS

From the study January 2015 to December 2017, a total of 430 FNAC's of breast were done.

The patients were from 13 to 100 years of age with a mean age was 38 years and median age was 35 years. Of 430 patients, 274 (63.72%) were ≤40 years of age, while 156 (36.28%) were >40 years of age. 21–30 years age group comprises most of the patient (118 = 27.44%) followed by 31–40 years age group (106 = 24.65%)

Of 430 patients, most patients (323 = 75.11%) had imaging before FNAC, while 107 = 24.89% had imaging after FNAC. Table 2 describes the initial imaging evaluation. Most patients had imaging with ultrasound (*n* = 344, 80%). The majority had diagnostic ultrasound (*n* = 292, 84.88%), while 52 (15.12%) had screening ultrasound. 86 = 20% patients imaged with mammography [Table 2].

The cytological spectrum of various palpable breast lesions in the present study shows that out of the total 430 cases, 300 (69.76%) were in the benign category, 10 (2.32%) were in the atypical category, 9 (2.09%) were in the suspicious category, and 99 (23.02%) belonged to the malignant category while the cytology study of 12 (2.79%) cases was unsatisfactory [Table 3].

Among the type of the lesions, fibroadenoma showed the highest (137 = 31.86%) incidence followed by carcinoma

Table 4: Frequency distribution of different categories of lesions according to age groups

Lesion Category	Diagnosis	Up to 20 years	21–30 years	31–40 years	41–50 years	51–60 years	>60 years	Total	%
Inflammation	Acute mastits	5	25	15	6	3	2	56	13.02
	Chronic nonspecific mastitis	0	4	2	0	0	0	6	1.3
	Chronic granulomatous mastitis	0	0	7	2	1	1	11	2.55
	Eosinophilic abscess	0	0	0	1	0	0	1	0.23
	Duct ectasia	0	1	0	0	0	0	1	0.23
	Fat necrosis	0	1	4	4	2	1	12	2.79
Cystic lesion	Galactocele	0	3	0	0	0	0	3	0.7
	Benign cystic lesion	1	6	4	2	2	0	15	3.48
	Fibrocystic disease	0	2	6	2	1	0	11	2.56
Benign neoplasm	Lactating adenoma	0	0	1	0	0	0	1	0.23
	Fibroadenoma	40	57	31	9	0	0	137	31.86
	Benign phyllodes	0	1	1	0	0	0	2	0.46
	Benign proliferative disease	3	2	5	3	1	0	14	3.25
Atypia	ADH	0	2	4	4	0	0	10	2.32
	Suspicious malignancy	0	1	3	1	2	2	9	2.09
Malignant neoplasm	Carcinoma/Lymphoma	0	2	15	38	20	24	99	23.02
Others	Fatty tissue	1	1	2	3	1	0	8	1.86
	Inadequate smears	1	3	4	4	0	0	12	2.79
	Normal breast tissue	3	5	0	1	0	0	9	2.09
	Gynaecomastia	2	1	1	2	0	4	10	2.32
	Lipoma	0	1	1	1	0	0	3	0.7
Total		56	118	106	83	33	34	430	100
%		13.02	27.44	24.65	19.3	7.67	7.9	100	

(99 = 23.02%) and benign cystic disease (15 = 3.48%) cases. Inflammatory lesions were acute mastitis 56 (13.02%), granulomatous mastitis 11 (2.55%), chronic mastitis 6 (1.3%), and fat necrosis 12 (2.79%). 42 (9.77%) cases designated as "others" included fatty tissue, lipoma, normal breast tissue, gynecomastia, and inadequate smears [Table 4].

The highest number of fibroadenoma (57) was in the age group of 21–30 years and <20 years group was second (40). Maximum of carcinoma cases were in the age group of 41–50 and 51–60 years of age group (38 and 20, respectively). Among the inflammatory lesions, the highest number was seen in the age group of 21–30 years group.

We found 11 (2.55%) cases of granulomatous mastitis. Among them, 4 (36.4%) were non-caseating and 7 (63.6%) were caseating consistent with tuberculosis. Ziehl–Neelsen stain of the suspected tuberculosis cases was done and found that 5 (45.45%) cases were positive for acid-fast bacilli (AFB) [Table 5].

The mean age of the suspicious for malignant cases was 48.2 ± 11.88 years, malignant cases was 53.4 ± 13.66 years, and benign cases was 32.0 ± 12.11 years [Table 6].

Regarding side involvement, almost in all cases, either the left or right side involvement was nearly equal [Table 7].

Mean lesion size of all 430 breast lesions was 3.37 ± 2.08 cm and mean lesion size of 99 malignant cases was 4.9 ± 2.21 cm. Among malignant lesions, 11.11% were presented with a size <2 cm, 67.67% with 2–5 cm, and 19.19% presented with >5 cm [Table 8].

The cytological spectrum of various malignant breast lesions encountered in the present study shows that out of the total 99 cases that could be satisfactorily labeled as malignant, infiltrating ductal carcinoma (IDC) accounted for 84 (84.84%) cases, mucinous carcinoma, poorly differentiated carcinoma, Paget's disease, neuroendocrine carcinoma, and sarcoma for 2 (2.22%) cases each, and

Table 5: Frequency distribution of types of granulomatous mastitis

Granulomatous inflammation	Frequency *n* (%)	AFB positive
Non-caseating granulomatous inflammation	4 (34.4)	Not done
Caseating granuloma consistent with tuberculosis	7 (63.6)	5
Total	11 (100)	5

AFB: Acid-fast bacilli

Table 6: Statistics of age (years) among different diagnoses

Cytological categories	Number	Mean±SD	Median	Range
C1 unsatisfactory	12	34.6±9.51	34.5	20–50
C2 benign	300	32±12.11	30	13–78
C3 atypia probably benign	10	38.2±7.47	39	26–50
C4 suspicious of malignancy	9	48.2±11.88	50	30–65
C5 malignant	99	53.4±13.66	50	30–100
Total	430	38±15	35	13–100

Table 7: Side involvement by different breast lesions

Cytological categories	Right *n* (%)	Left *n* (%)	Bilateral *n* (%)	Total
C1 unsatisfactory	04 (33.33)	05 (41.66)	03 (25)	12
C2 benign	128 (42.66)	152 (50.66)	20 (6.66)	300
C3 atypia probably benign	03 (30)	07 (70)	0	10
C4 suspicious of malignancy	03 (33.33)	04 (44.44)	02 (22.22)	09
C5 malignant	52 (52.52)	47 (47.47)	0	99
Total	190 (44.18)	215 (50)	25 (5.81)	430

Table 8: Size of malignant breast lesions

Malignant breast lesion	Size of the malignant breast lesion (%)			Total	Palpable axillary LN
	<2 cm	2–5 cm	>5 cm		
Ductal carcinoma (NOS)	9 (10.7)	57 (67.85)	16 (19.04)	84	25
Other carcinomas/lymphoma/sarcoma	02 (13.33)	10 (66.66)	03 (20)	15	02
Total	11 (11.11)	67 (67.67)	19 (19.19)	99	27

medullary carcinoma, lobular carcinoma, carcinoma with osteoclastic type giant cell, metaplastic, and lymphoma for 1 (1.53%) case each [Figure 1].

Among 99 malignant cases, only 27 showed palpable axillary lymph nodes and 12 (12.12%) cases of these showed the presence of metastasis and rest 15 (15.15%) were reactive lymph nodes [Table 9].

DISCUSSION

The study population ranged from 13 to 100 years with a mean age of 38 years. Rahman and Islam,[7] from Bangladesh, reported 14–86 years with a mean age of 33.6 years. Ahmed *et al.*,[8] from Sudan, reported 15–85 years of age range with a mean of 37 years. Bukhari *et al.*[9] showed a range of 16–70 years in Pakistan, Kumar[10] reported 6–72 years and Tiwari[11] 17–56 years in Nepal with a mean age of 34 and 32 years, respectively, and 18–92 years with a mean age of 59.3 years were reported by Dennison *et al.*[12] in the United Kingdom (UK). The higher mean age of this study from Nepal, Pakistan, and Bangladesh may be explained by the increased life expectancy rates from those countries. Again the lower mean age from the study of the UK is also may be due to lower life expectancy rate of India compared to the UK.

In this study, the lesion presented in the right breast was 44.19%, the left breast was 50.00%, and 5.81% of cases involved bilateral breast that was similar to the study of Rahman and Islam[7] in which the right breast was 49.05%, the left breast was 47.55%, and 3.4% of cases involved both. Kumar[10] observed a deviation from our results with a little predominance of the right breast (51.4%). This might an incidental finding and it required very large group population-based study to find out any significant difference. Regarding malignant cases, we observed 52.52% of cases involved the right side, 47.47% involved the left, and none involved both. Similar to the study of Rahman and Islam[7] 49.60% of cases involved the right side, 48.81% involved the left, and 1.59% involved both, and Sankaye and Dongre[13] and Rupom *et al.*[14] found 58.18% of malignant lesion in the right breast. This is in contrast with the findings of Meena *et al.*,[15] Reddy and Reddy,[16] and Clegg-Lamptey and Hodasi[17] in which the left side was slightly more common.

The present study shows similar case distribution that of Sankaye *et al.*[14] but accounted for less number of benign cases and more number of malignant cases than Mohammed *et al.*[18] Yeoh and Chan,[19] Park and Ham,[20] Rocha *et al.*,[21] and Domínguez *et al.*[22] Incidence of suspicious lesions and atypical lesions in the present study is almost same as that in other studies. Although the finding of unsatisfactory lesions in the present study is more than in the study by Mohammed *et al.*,[18] it, still, is much less than the majority of other studies, Table 10.

Among the granulomatous mastitis, we found that 5 (45.45%) cases were positive for AFB and Rahman and Islam[7] found 12 cases positive for AFB (12/116).

Fibroadenoma was the major, 31.86%, cause of the breast lump in this study; findings were similar to 28.57% of Rahman and Islam,[7] 28% of Ahmed *et al.*,[8] and near similar to the findings of Kumar[10] 22%. Besides, Bukhari *et al.*[9] showed 16% and Pradhan and Dhakal[23] showed only 8% of fibroadenoma cases.

A total number of 10 (2.32%) cases of atypical ductal hyperplasia (ADH) and 9 (2.09%) cases of suspicious for malignancy were found. Rahman and Islam[7] reported 1.12% of cases of ADH and 1.60% of cases of suspicious for malignant cells. Pradhan and Dhakal[23] reported 2.3% and Ahmed *et al.*[8] 2.5%.

Considering malignant cases, we found 99 (23.02%) malignant breast lesion, of these, 84 (84.84%) were ductal carcinoma. Rahman and Islam[7] found 252 (14.17%) carcinoma cases, among which 251 cases were ductal carcinoma and only

Table 9: Axillary lymph node status in the carcinoma patients

Lymph Node	Number of cases (%)
Metastatic	12 (12.12)
Reactive	15 (15.15)
Not palpable	74 (74.74)
Total	99 (100)

Table 10: Cytological cases comparative study

Cytological type	Present study (%)	Sankay *et al.*[13] (%)	Mohammed *et al.*[18] (%)	Yeoh and Chan[19] (%)	Park and Ham[20] (%)	Rocha *et al.*[21] (%)	Dominguez *et al.*[22] (%)
C1 unsatisfactory	12 (2.79)	13 (5.77)	3 (1.9)	274 (17.83)	169 (25.3)	71 (8.77)	142 (10.15)
C2 benign	300 (69.76)	131 (58.22)	112 (71.3)	1121 (73.12)	384 (57.4)	615 (76.02)	1087 (77.75)
C3 atypia probably benign	10 (2.32)	8 (3.55)	2 (1.3)	51 (3.32)	24 (3.6)	-	-
C4 suspicious of malignancy	09 (2.09)	8 (3.55)	2 (1.3)	19 (1.23)	7 (1.0)	26 (3.21)	20 (1.14)
C5 malignant	99 (23.02)	65 (28.88)	38 (24.2)	68 (4.43)	85 (12.7)	97 (12)	149 (10.65)
Total	430	225	157	1533	669	809	1398

one was lobular carcinoma. Sankaye and Dongre[13] found 65 (28.8%) malignant lesions, IDC was most common 55 (88.60%) and mucinous carcinoma was the second most common tumor in there study with 4 (6.15%) cases while in the study by Domínguez *et al.*[22] 147 malignant cases were seen, 141 (95.91%) were IDC and lobular carcinoma was the second common tumor in the study by Domíngue *et al.* with 4 (2.72%) cases.[22] We found mucinous carcinoma, poorly differentiated carcinoma, Paget's disease, neuroendocrine carcinoma, and sarcoma for 2 (2.22%) cases each, and medullary carcinoma, lobular carcinoma, carcinoma with osteoclastic type giant cell, metaplastic, and lymphoma for 1 (1.53%) case each. Diagnosis was made as per literature.[24-34]

CONCLUSION

Primary categorization of breast lumps into unsatisfactory, benign, inflammatory, atypical/suspicious, and malignant categories can be done by FNAC. FNAC is a cheaper, rapid, less invasive, and effective method. Benign breast lesions are common than malignant lesions, fibroadenoma for benign disease, whereas IDC accounts for the highest number of malignant lesions.

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Original Article

Comparison of Efficacy of the Anti-inflammatory Effect of Topical 0.1% Dexamethasone Sodium and Topical 0.05% Difluprednate Eye Drops after Small Incision Cataract Surgery

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Abstract

Aims: The study aims to compare the efficacy of the anti-inflammatory effect of 0.1% dexamethasone sodium and 0.05% difluprednate eye drops after small incision cataract surgery (SICS).

Study Design: A prospective, randomized, and clinical study was conducted on patients.

Place and Duration of Study: This study was conducted in the Department of Ophthalmology, VCGS Government Medical College, Srinagar, Uttarakhand, between December 2017 and November 2018.

Materials and Methods: This study included two groups of 40 patients each (a total of 80 patients). 40 patients in Group A were randomly started on 0.1% dexamethasone eye drops postoperatively and another 40 patients in Group B were randomly started 0.05% difluprednate eye drops postoperatively. Response to the therapy was recorded on day 1, 7, and 40 on the parameters of post-operative anterior chamber reaction and post-operative visual acuity, and the results were compared.

Results: All results were correlated with final visual outcome, and post-operative flare, which showed 0.05% difluprednate, is clinically and statistically more effective in early post-operative period than 0.1% dexamethasone sodium to control inflammation in uneventful SICS.

Conclusions: After the comparison of the data in both the groups, the patients started on 0.05% difluprednate eye drops postoperatively showed better response to therapy ($P < 0.0001$) with respect to the parameters of best-corrected visual acuity and post-operative flare as compared to the patients started on 0.1% dexamethasone sodium eye drop therapy postoperatively, indicating that 0.05% difluprednate eye drops have a better anti-inflammatory effect.

Key words: Anti-inflammatory effect, Cataract surgery, Dexamethasone, Difluprednate

INTRODUCTION

Cataract surgery is, with >20–25 million procedures estimated annually, the most performed surgical intervention worldwide. Due to the invasive nature of modern cataract surgery, two outcomes are common: Infection and intraocular inflammation.[1] Infection, while an area of great concern and somewhat controversial in the ways to prevent it, is a long discussion delving into topics such as intracameral and post-operative care.[2]

Intraocular inflammation occurs due to the breakdown of cell membranes as a result of tissue injury. In effect, an inflammatory cascade occurs that involves the step-by-step enzymatic conversion of cell membrane phospholipids to bioactive prostaglandin molecules. First, surgical trauma activates phospholipase A2, which releases arachidonic acid from membrane phospholipids (fats from the lipid bilayer).

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Arachidonic acid is then metabolized by cyclooxygenase (COX-1 and COX-2) into unstable endoperoxide intermediates (prostaglandin G2 and prostaglandin H2). This ultimately leads to the formation of prostaglandins. Prostaglandin H2 is then isomerized into different prostanoids.[3] All of these lead to local vasodilation and increased vascular permeability. This results in a number of symptoms including hyperemia, miosis, pain, photophobia, diminished visual acuity, and cystoids macular edema.[1] Inflammation is classically treated with steroids as well as with nonsteroidal anti-inflammatory drugs (NSAIDs).[4] NSAIDs drugs, in particular, reduce inflammation and pain by blocking prostaglandin synthesis by inhibiting COX activity.[5]

Treatment using topical NSAIDs after cataract surgery began in the 1970s[6] and studies have shown that they offer efficacy comparable to steroids in reducing post-operative inflammation but with a lower risk for adverse events in most patients.[1] NSAIDs drugs play a number of important roles in post-operative care including management of macular leakage.[7]

Visual prognosis of patient after cataract surgery depends on various pre-operative, intraoperative, and post-operative factors, of which postsurgical inflammation is the most important factor to the ophthalmologists. This postsurgical inflammation is due to various intraocular manipulations as irrigation of anterior chamber, injection of viscoelastic agent, handling of iris, intraocular lens implantation, etc.[8]

Ocular inflammation after cataract surgery presents ophthalmologists with treatment dilemma. While corticosteroids are traditionally the therapy of choice for inflammation, their long-term use for managing ocular inflammation can produce significant adverse effects.

The present study is an effort to compare the anti-inflammatory efficacy of post-operative 0.1% dexamethasone and 0.05% difluprednate eye drops in patients undergoing small incision cataract surgery (SICS).

MATERIALS AND METHODS

This prospective, randomized, and clinical study was conducted on patients attending the eye outpatient department of VCSG Government Medical College, Srinagar, Uttarakhand, India, during December 2017–November 2018.

A total of 80 patients who underwent SICS with posterior chamber intraocular lens (IOL) implantation were studied and patients were divided into two groups.

Group-A

It comprised 40 patients who received 0.1% dexamethasone eye drops 1 hourly 8 times a day for 7 days then tapered till 40 days.

Group-B

It comprised 40 patients who received 0.05% difluprednate eye drops 1 hourly 8 times a day for 7 days then tapered till 40 days.

Informed consent was obtained from all participant and associated adverse effects of the drug were explained.

Inclusion Criteria

Uncomplicated senile cataract, no previous ocular surgery, no previous ocular disease, not allergic to any drug, and uncomplicated SICS with in bag IOL implantation were included in the study.

Exclusion Criteria

Bleeding disorders, hypertension, diabetes mellitus, ischemic heart disease, bronchial asthma, connective tissue disorder, and poor compliance were excluded from the study. Preoperatively, all patients underwent visual acuity testing, measurement of intraocular pressure, and detailed slit lamp examination. All patients were operated by a single surgeon using similar instruments and techniques.

The post-operative medication was administered 8 times a day for 1 week and later tapered to 3 times a day for rest of the period. Both groups received topical mydriatic and cycloplegic agent as homatropine 2% once a day. Post-operative patients were followed up for 6 weeks at day 1, 7, and 40. Grading of post-operative inflammation was done on the following observations: Circumcorneal congestion, corneal edema, anterior chamber cells, and flare. Analgesia was subjectively estimated based on patients complaint of pain and discomfort.

RESULTS

Almost all patients in both groups had pain, lid edema, and ciliary congestion on the first 2 post-operative days.

Age

After comparing the data in both the groups [Table 1 and Figure 1], mean age of patients in Group A was 62.80 ± 11.47 while the age in Group B was 65.23 ± 11.23.

Sex Distribution and Laterality

In Table 2 and Figure 2, both groups had equal distribution of male and female genders. According to Table 3 and

Figure 3, majority patients in Group A had undergone surgery in the right eye, whereas in Group B, this was equal for both the eyes.

Day 1 Flare

According to Table 4 and Figure 4, majority of patients in Group A (52.50%) had moderate flare and same was the case for Group B (62.50%).

Day 7 Flare

According to [Table 5 and Figure 5] majority of patients in group A (70%) had moderate flare and same was the case in group B (77.50%)

Day 40 Flare

According to Table 6 and Figure 6, Group A had majority of patients with moderate flare, whereas Group B had majority of patients in the mild flare category ($P < 0.0001$).

Uncorrected Visual Acuity (UCVA) (Day 1)

According to Table 7 and Figure 7 in Group A, majority (62.50%) patients had visual acuity in the range 6/24–6/60 and the number was same in Group B.

Uncorrected Visual Acuity (Day 7)

According to [Table 8 and Figure 8] in Group A, majority(60%) patients had visual acuity in range 6/24-6/60 and in Group B Majority (70%) had visual acuity in range of 6/18-6/6

Best-corrected Visual Acuity (BCVA) (Day 40)

According to Table 9 and Figure 9, Group A had maximum patients (60%) in the range of 6/24–6/60, whereas in Group B, the maximum patients belonged to the range of 6/18–6/6 ($P < 0.0001$).

Change between UCVA (Day 1) and BCVA (Day 40)

Mean change in visual acuity in Group A [Table 10 and Figure 10] was 86.33%, whereas the same change

Table 1: Group comparison for age distribution (years)

Age (years)	Number of patients	
	Group A (*n*=40)	Group B (*n*=40)
≤50	7 (17.50)	4 (10.00)
51–60	9 (22.50)	7 (17.50)
61–70	15 (37.50)	20 (50.00)
>70	9 (22.50)	9 (22.50)
Mean age±SD	62.80±11.47	65.23±11.23
P-value	0.223	

SD: Standard deviation

Table 2: Sex distribution

Sex	Number of patients	
	Group A (*n*=40)	Group B (*n*=40)
Male	20 (50.0)	20 (50.0)
Female	20 (50.0)	20 (50.0)
P-value	–	

Table 3: Laterality

Eye	Number of patients	
	Group A (*n*=40)	Group B (*n*=40)
Right eye	25 (62.50)	20 (50.0)
Left eye	15 (37.50)	20 (50.0)
P-value	0.071	

Table 4: Day 1 flare

Day 1 flare	Number of patients	
	Group A (*n*=40)	Group B (*n*=40)
Mild flare	10 (25.00)	6 (15.00)
Moderate flare	21 (52.50)	25 (62.50)
Severe flare	9 (22.50)	9 (22.50)
P-value	0.192	

Table 5: Day 7 flare

Day 7 flare	Number of patients	
	Group A (*n*=40)	Group B (*n*=40)
Mild flare	12 (30.00)	8 (20.00)
Moderate flare	28 (70.00)	31 (77.50)
Severe flare	0 (0.00)	1 (2.50)
P-value	0.092	

Table 6: Day 40 flare

Day 40 flare	Number of patients	
	Group A (*n*=40)	Group B (*n*=40)
Mild flare	17 (42.50)	32 (20.00)
Moderate flare	23 (57.50)	8 (80.00)
Severe flare	0 (0.00)	0 (0.00)
P-value	<0.0001	

Table 7: UCVA (day 1)

UCVA	Number of patients	
	Group A (*n*=40)	Group B (*n*=40)
≤6/18–6/6	4 (15.00)	17 (42.50)
6/24–6/60	25 (62.50)	23 (57.50)
5/60≥	11 (27.50)	0 (0.00)
P-value	<0.0001	

UCVA: Uncorrected visual acuity

Table 8: UCVA (day 7)

UCVA	Number of patients	
	Group A (*n*=40)	Group B (*n*=40)
≤6/18–6/6	11 (27.50)	28 (70.00)
6/24–6/60	24 (60.00)	12 (30.00)
5/60≥	5 (12.50)	0 (0.00)
P-value	<0.0001	

UCVA: Uncorrected visual acuity

was recorded as 59.03% in Group B. This change was statistically significant ($P < 0.0001$).

Change Between Ucva Day 7 and (BCVA) (Day 40)

Mean change in visual acuity in Group A [Table 11 and Figure 11] was 43.75%,Whereas the same change was recorded as 28.41% in Group B. P<0.0001

DISCUSSION

Topical steroids are the most common methods of administering steroids to the eye and following a single topical drop, steroid is measurable in human aqueous humor within 15–30 min.[9] They are the main drugs that have been used so far for controlling post-operative inflammation after intraocular surgery. Steroids act by inhibiting production of factors (prostaglandins, leukotrienes, etc.), which are critical in generating the inflammatory response by multiple type of cells. When applied topically, the drug has to penetrate the cornea across the three barriers: Corneal epithelium-lipophilic in nature, corneal stroma-hydrophilic, and endothelium lipophilic. Leopold *et al.*[10] showed that lipophilic layers of cornea provide resistance to polar molecules, whereas stroma being hydrophilic has resistance for lipid-soluble molecules; hence, substance used should be of biphasic polarity. Studies of Leibowitz *et al.*[11] with radiolabelled dexamethasone and prednisolone have shown that acetate in the form of suspension can penetrate through a normal and uninflammed cornea with an intact epithelium most easily and can attain the maximum concentration of 2336 μg/min/g within 30 min of topical application in anterior chamber.[12]

Schoenwald and Boltralik[13] also showed in experimental animals that prednisolone acetate suspension reaches the higher corticosteroid levels in anterior chamber among the other drugs used.

Table 9: BCVA (day 40)

BCVA (day 40)	Number of patients	
	Group A (*n*=40)	Group B (*n*=40)
≤6/18–6/6	16 (40.00)	33 (82.50)
6/24–6/60	24 (60.00)	7 (17.50)
5/60≥	0 (0.00)	0 (0.00)
P-value	<0.0001	

BCVA: Best-corrected visual acuity

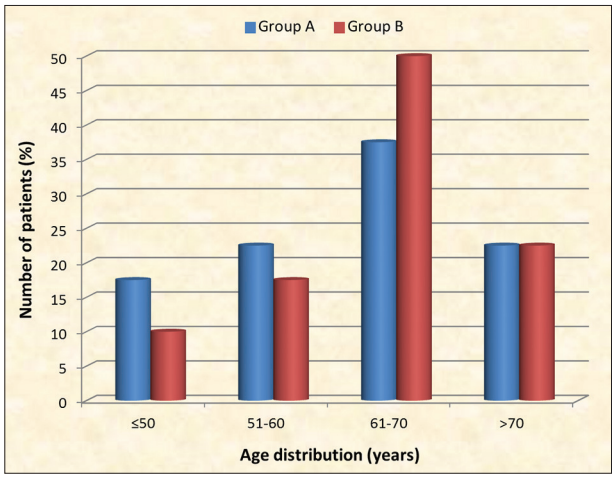

Figure 1: Age distribution (years)

Table 10: Change between UCVA (day 1) and BCVA (day 40)

Visual acuity	Number of patients					
	Group A (*n*=40)			Group B (*n*=40)		
	UCVA (day 1)	BCVA (day 40)	Change (%)	UCVA (day 1)	BCVA (day 40)	Change (%)
≤6/18–6/6	4 (15.00)	16 (40.00)	75.00	17 (42.50)	33 (50.0)	48.48
6/24–6/60	25 (62.50)	24 (60.00)	84.00	23 (57.50)	7 (50.0)	69.57
5/60≥	11 (27.50)	0 (0.00)	100.00	0 (0.00)	0 (50.0)	0.00
Mean change	86.33			59.03		
P-value	<0.0001					

UCVA: Uncorrected visual acuity, BCVA: Best-corrected visual acuity

Table 11: Change between UCVA (day 7) and BCVA (day 40)

Visual acuity	Number of patients					
	Group A (*n*=40)			Group B (*n*=40)		
	UCVA (day 7)	BCVA (day 40)	Change (%)	UCVA (day 7)	BCVA (day 40)	Change (%)
≤6/18–6/6	11 (27.50)	16 (40.00)	31.25	28 (70.00)	33 (82.50)	15.15
6/24–6/60	24 (60.00)	24 (60.00)	0.00	12 (30.00)	7 (17.50)	41.67
5/60≥	5 (12.50)	0 (0.00)	100.00	0 (0.00)	0 (0.00)	0.00
Mean change	43.75			28.41		
P-value	<0.0001					

UCVA: Uncorrected visual acuity, BCVA: Best-corrected visual acuity

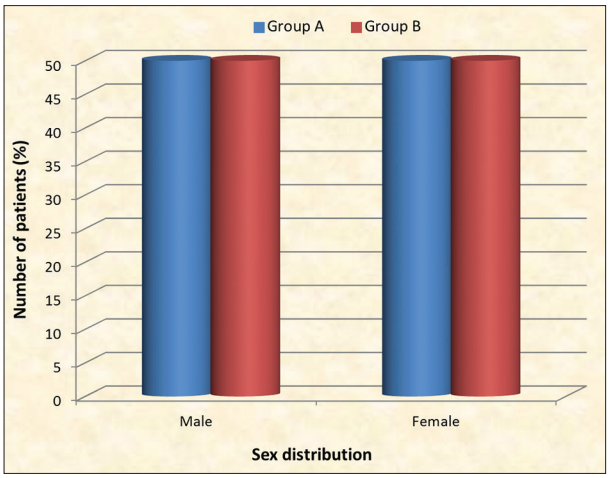

Figure 2: Sex distribution

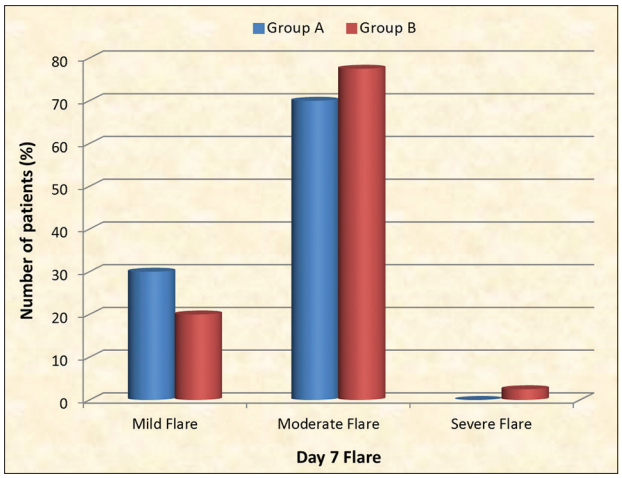

Figure 5: Day 7 flare

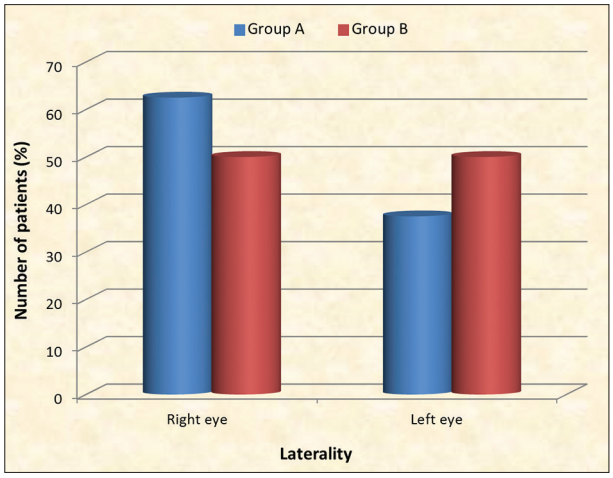

Figure 3: Laterality

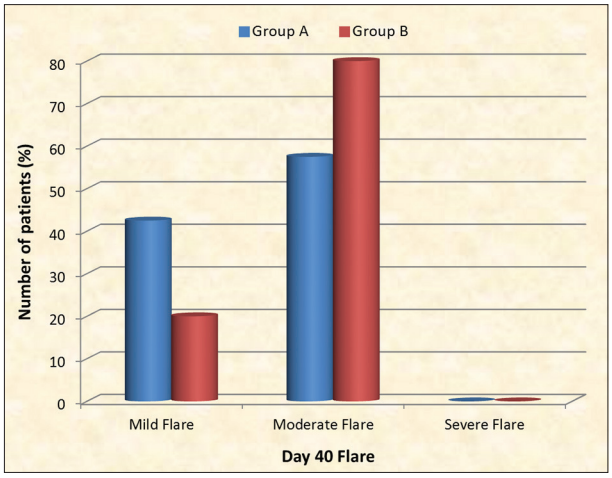

Figure 6: Day 40 flare

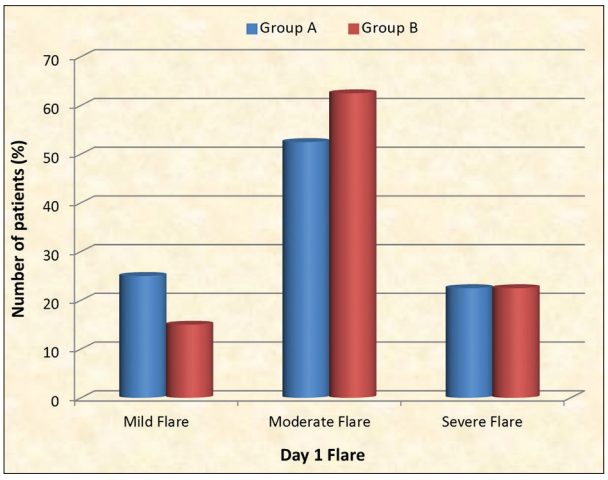

Figure 4: Day 1 flare

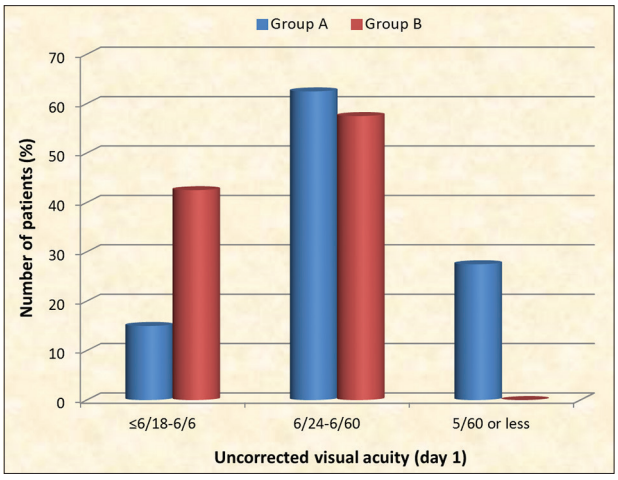

Figure 7: Uncorrected visual acuity (day 1)

The bioavailability and effectiveness of the anti-inflammatory drugs were studied by Leibowitz *et al.* [12] using radiolabeled polymorph nuclear leucocytes systemically before they invade the cornea. Commercially available preparation used for the present study of 0.05% difluprednate in the form of suspension and dexamethasone was 0.5% dexamethasone sodium solution.

Difluprednate acts by inhibiting the action of phospholipase A2 and thereby preventing the release of arachidonic

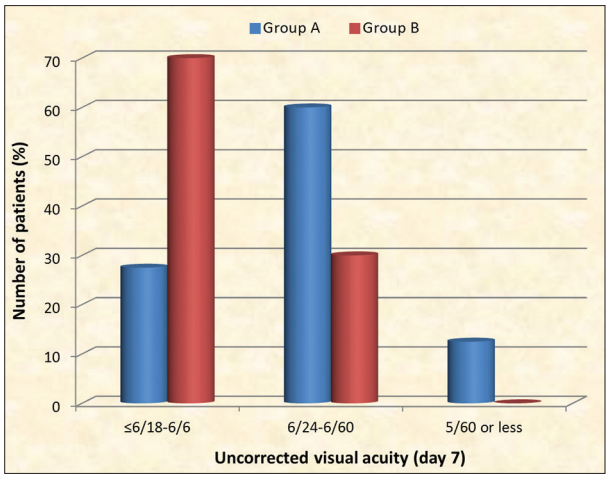

Figure 8: Uncorrected visual acuity (day 7)

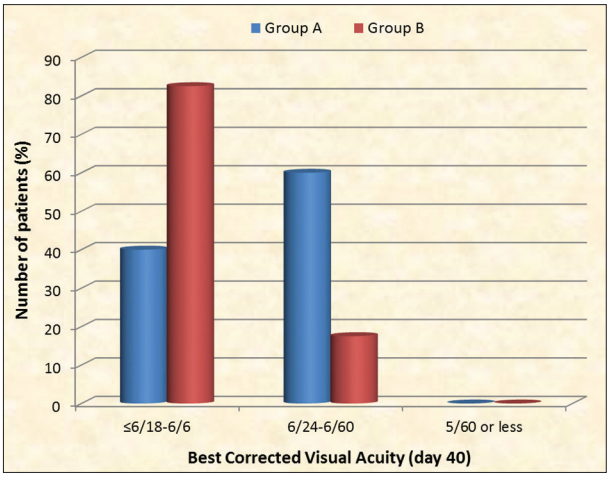

Figure 9: Best-corrected visual acuity (day 40)

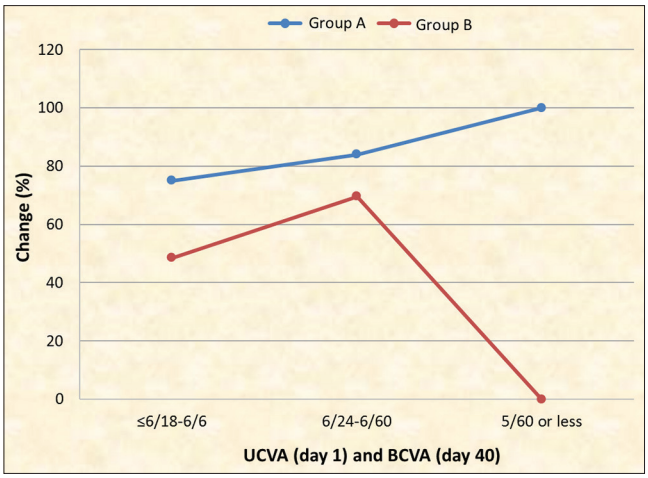

Figure 10: Uncorrected visual acuity (day 1) and best-corrected visual acuity (day 40)

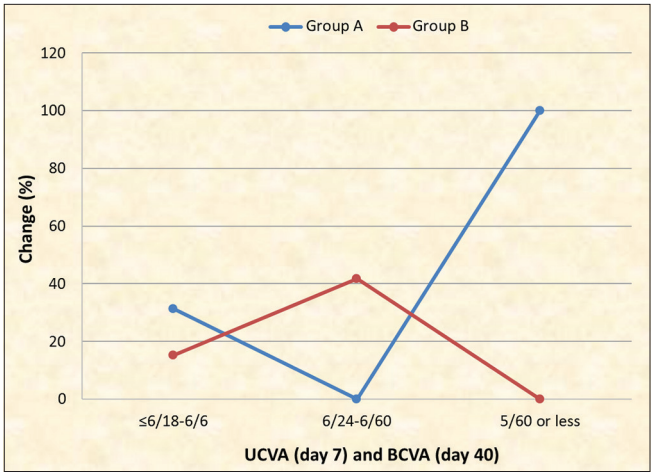

Figure 11: Uncorrected visual acuity (day 7) and best-corrected visual acuity (day 40)

acid, which, in turn, is responsible for formation of prostaglandin and leukotrienes. Prednisolone acetate is 4 times potent than cortisol and also has mineralocorticoid activity. The half-life is 12 h and is less toxic as compared to dexamethasone sodium.

The experimental data put forth by Leibowitz and Kupferman,[10] with studies *in vivo* showed that prednisolone acetate being biphasic in nature attains a maximum conc. of 2336 μg in anterior chamber with epithelium intact which shows that its acetate form is more potent than its phosphate form which shows a conc. of 968 μg. Similar results were obtained by O lejnika and Weisbecker.[14]

Furthermore, according to the present study, 0.05% difluprednate had better effects in controlling post-operative inflammation than 0.1% dexamethasone with regard to the parameters in consideration, i.e., post-operative visual acuity and post-operative flare.

CONCLUSIONSW

The present study concludes that the post-operative anti-inflammatory potency of 0.05% difluprednate is statistically better than 0.1% dexamethasone sodium eye drops. This study recommends the use of topical 0.05% difluprednate to control inflammation after uneventful cataract surgery in Indian eyes. The effect of 0.05% difluprednate was not studied on cataract surgery with pre-operative complications; hence, its effect in treating such eyes is not known.

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Original Article

Comparative Evaluation of Pre-operative MDCT Findings and Intraoperative ESS Findings with Regard to Osteomeatal Complex in Patients With Chronic Rhinosinusitis

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Abstract

Background and Objective: Background and objective of the study were to determine how well the pre-operative multidetector-row computed tomography (MDCT) findings and intraoperative endoscopic sinus surgery findings correlate in patients with chronic rhinosinusitis (CRS) and to assess the various anatomical variations of the osteomeatal complex in these patients.

Materials and Methods: A total of 100 patients falling within the inclusion criteria with diagnosed CRS who had given consent for participating in this study were analyzed. The study period was from January 2016 to December 2016. In these patients, a detailed history and examination were done, counseled regarding the necessity of MDCT scan imaging of the nose and sinuses and further about the need for endoscopic evaluation and functional endoscopic sinus surgery (FESS). Scans were evaluated preoperatively as per Lund–Mackay CT scan score and anatomic variants regarding OMC were noted. Later, intraoperative findings were noted, and kappa statistics was used to analyze the agreement between MDCT and intraoperative endoscopic findings.

Results: Agger nasi, concha bullosa, medial and lateral deviation of the uncinate process and paradoxical middle turbinate showed a very good correlation of agreement between pre-operative CT scan and operative findings. Excellent correlation was found in case OMC obstruction, and there was a very good correlation of agreement between pre-operative CT scan and operative findings.

Conclusion: MDCT shows an increased sensitivity compared to routine CT in detecting OMC obstruction, and it had a very good correlation with intraoperative findings. There was an excellent correlation between MDCT and intraoperative findings in cases of all anatomic variants studied except concha bullosa. In conclusion, MDCT can help clinicians to better predict the OMC status pre-operatively and thereby guide FESS.

Key words: Chronic rhinosinusitis, Multidetector-row computed tomography, Osteomeatal complex

INTRODUCTION

Chronic rhinosinusitis (CRS) is one of the most common causes of a headache for which consultation of an otorhinolaryngologist is sought for. It affects a major proportion of the population worldwide and causes significant physical symptoms and emotional impairment adversely affecting the quality of life.

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The endoscopic sinus surgery is a minimally invasive technique which aims mainly at the removal of diseased mucosa and any pathology causing the obstruction of the osteomeatal complex, resulting in re-establishment of mucociliary drainage, and ventilation of paranasal sinuses.

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Computer tomography (CT) scan is the method of choice for evaluation of paranasal sinuses before surgery, and the coronal plane is the preferred imaging plane because it displays the osteomeatal complex the best. Safe, meticulous, and complete endoscopic surgery can be performed only after interpreting the CT scan, which gives detailed bony anatomy of the area. There is a high correlation between findings of CT examination and intraoperative endoscopic findings, but there are discrepancies also. In several studies, the findings that suggested sinus disease were intraoperatively seen polyps, purulent discharge, and edematous mucosa. Prospective studies of endoscopy demonstrate a sensitivity and specificity of 75% and 84%, respectively, when correlated with pre-operative routine CT for CRS. Technical developments in computer-assisted tomography such as multidetector-row CT (MDCT) help the surgeon in increasing diagnostic accuracy. Axial MDCT with secondary multiplanar reformation provides the necessary pre-operative information regarding the extent of disease and sinus anatomy. Routine head CT has an effective dose of 1–2 mSv to the whole body. The standard-dose MDCT protocol delivered a radiation dose of 0.70 mSv in men and 0.76 mSv in women. Hence, MDCT of paranasal sinus possesses the potential for a reduction in the radiation dose by 20%.

This study is undertaken to find out how well the pre-operative MDCT findings correlate with intraoperative endoscopic sinus surgery findings and to recognize the anatomical variations of osteomeatal complex region.

Objective of the Study

The objective of the study was to determine how well the pre-operative MDCT findings correlate with the intraoperative endoscopic sinus surgery findings with regard to osteomeatal complex, in patients undergoing functional endoscopic sinus surgery (FESS) for CRS unresponsive to medical management, and to assess the distribution of anatomic variants related to osteomeatal complex in this study population.

MATERIALS AND METHODS

A prospective study of 100 patients with clinical diagnosis of CRS, refractory to medical management and planning for FESS was done in the Department of ENT, Sree Gokulam Medical College, and Research Foundation from January 2016 to December 2016. Patients with the previous alteration of the paranasal sinus anatomy due to facial trauma, aggressive fungal infection, infiltrating tumors, and pregnant patients were excluded. In these patients, a detailed history and examination were done, counseled regarding the necessity of MDCT scan imaging of the nose and sinuses and further about the need for endoscopic evaluation and FESS. Informed consent was taken from all the cases, and data regarding the patients were collected. Scans were taken and evaluated preoperatively as per Lund–Mackay CT scan score. Later, intraoperative findings were noted, and the data were coded and entered to Microsoft Excel, analyzed using SPSS software by means of kappa statistics to determine the agreement between pre-operative MDCT and intraoperative endoscopic findings.

RESULTS AND ANALYSIS

In this study, data regarding sociodemographic variables such as age and sex were collected.

The mean age of the study population was 35.15 ± 13.48 years. The highest number of patients was in the range of 30–60 years. The percentage of males (53%) was found to be more than females (47%). 10% of patients had undergone previous sinus surgery, now needing revision surgery.

The most common presenting symptom in the study population nasal obstruction (100%) which was present in all patients in this study group. It was followed by nasal discharge/purulence/discolored postnasal discharge (91%), cough (79%), headache and facial pain (73%), dental pain (64%), and facial congestion/fullness (63%). Less common symptoms were fatigue (16%), hyposmia (14%), halitosis (11%), ear pain/pressure/fullness (10%), and purulence on nasal cavity examination (5%).

On doing MDCT peripheral nervous system (PNS), maxillary (93%) and anterior ethmoid sinuses (93%) were found to be the most commonly involved sinuses, followed by posterior ethmoid sinuses (79%) and frontal sinuses (66%). Sphenoid sinus (58%) was the least involved sinuses radiologically. OMC was obstructed in 44% of the study group.

Analyzing the MDCT, Lund and Mackay scores of CRS showed that a maximum number of 41 (41%) patients had score between 11 and 15 and minimum number of 1 patient had their scores between 21 and 24. The mean score was 9.52 ± 3.76.

Comparative Assessment of Anatomical Variants Regarding OMC on MDCT and FESS

In MDCT, the most common anatomical variant was agger nasi seen in 72% of the study population followed by concha bullosa (53%). The least common anatomical variant with regard to OMC was Haller's cell seen in only 9% of the study population. Intraoperatively, the most

common anatomical was agger nasi seen in 72% of the study population followed by concha bullosa (61%) and the least common anatomical variant with regard to OMC was Haller's cell seen in only 5% of the study population [Table 1 and Graph 1].

Excellent correlation was found in cases of agger nasi, medial and lateral deviation of the uncinate process, paradoxical middle turbinate and Haller's cell. Correlation was good for concha bullosa. Agger nasi, concha bullosa, medial and lateral deviation of uncinate process, and paradoxical middle turbinate showed a very good correlation of agreement between pre-operative CT scan and operative findings, while Haller's cell showed a good correlation of agreement [Table 2]. In our study, all parameters except Haller's cell were statistically significant [Table 2].

Table 1: Comparative assessment of anatomical variants with regard to OMC MDCT versus ESS

Anatomical variants	MDCT	ESS
	n (%)	*n* (%)
Agger nasi	72 (72.0)	72 (72.0)
Concha bullosa	53 (53.0)	61 (61.0)
Medial deviation of uncinate process	26 (26.0)	26 (26.0)
Lateral deviation of uncinate process	13 (13.0)	13 (13.0)
Paradoxical middle turbinate	13 (13.0)	13 (13.0)
Haller's cell	9 (9.0)	5 (5.0)

MDCT: Multidetector-row Computed tomography, ESS: Endoscopic sinus surgery

Comparative Assessment of Other Sinus Related Findings

The other sinus related finding we studied was OMC obstruction which shoes a prevalence of 44% in MDCT and a prevalence of 43% intraoperatively [Table 3 and Graph 2].

Excellent correlation was found in case OMC obstruction, and there was a very good correlation of agreement between pre-operative CT scan and operative findings [Table 4]. $P < 0.05$ was statistically significant [Table 4].

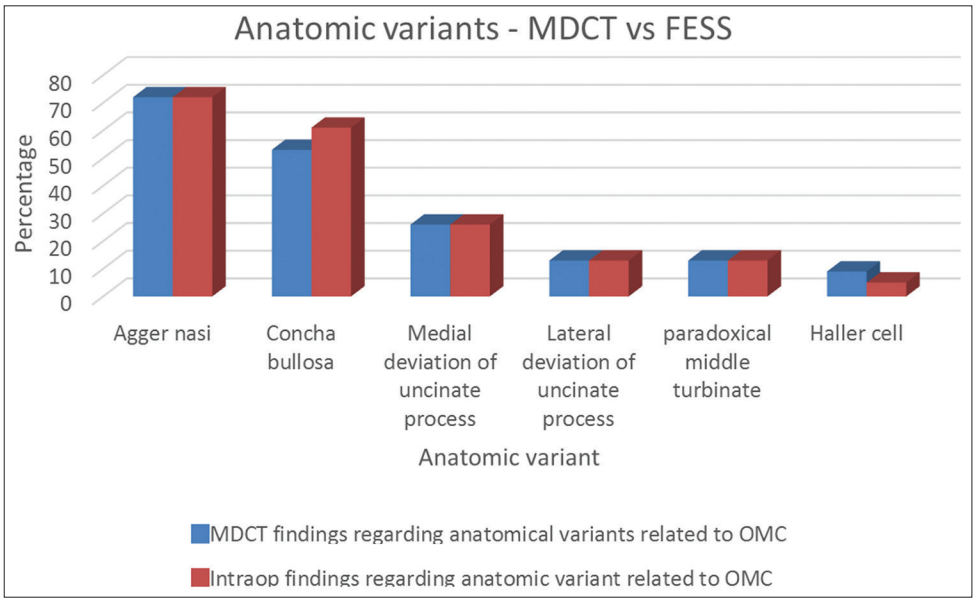
DISCUSSION

Pathogenesis of sinusitis was a point of interest from 17th century onward. In the early 19th century, Zuckerkandl

Table 2: Correlation between preoperative MDCT scan and endoscopic sinus surgery findings in chronic sinusitis with regard to anatomical variants

Anatomical variant	Sensitivity	Specificity	PPV	NPV	Correlation	κ	Agreement	*P* value	Statistical significance
Agger nasi	100	100	100	100	Excellent	1	Very good	<0.01	Significant
Concha bullosa	86.9	100	100	82.97	Good	0.838	Very good	<0.01	Significant
Medial deviation of uncinate process	100	100	100	100	Excellent	1	Very good	<0.01	Significant
Lateral deviation of uncinate process	100	100	100	100	Excellent	1	Very good	<0.01	Significant
Paradoxical middle turbinate	100	100	100	100	Excellent	1	Very good	<0.01	Significant
Haller's cell	100	95.8	55.6	100	Excellent	0.695	Good	0.142	Insignificant

PPV: Positive predictive values, NPV: Negative predictive values, MDCT: Multidetector-row Computed tomography. *Sensitivity of - > 90 is excellent correlation, > 80 is good correlation, > 70 is acceptable, > 60 is poor correlation. †Kappa's value: 0.81–1.0 is very good agreement between CT scan and operative findings, 0.61–0.80 is good agreement, 0.41–0.60 is moderate agreement, 0.21–0.40 is fair agreement, <0.2 is poor agreement



Graph 1: Percentage distribution of anatomical variants with regard to OMC detected by multidetector-row computed tomography versus endoscopic sinus surgery

described pathologies affecting paranasal sinuses.[1] Open approaches to the maxillary sinus were first described as early as the 18th century. The Caldwell-Luc procedure was described in 1893 by George Caldwell and further elucidated in France by Henri Luc in 1897.[2] The first attempt at nasal endoscopy was made by Hirshman in 1901, using a modified cystoscope.[3] Endoscopic sinus surgery was introduced in Europe by Messerklinger in 1967. In 1985, Kennedy introduced the technique of FESS into the United States.[4] It was not until the middle of 20th century that Professor H. Hopkins developed rod optic telescope, following which endoscopes incorporating fiber optic light delivery and rod optical system which opened up the possibility of routine endoscopic examination of the nose and paranasal sinuses.[5] Stammberger explained the role of diagnostic nasal endoscopy and computed tomography (CT) in sinus surgery leading to the concept of image-guided surgery in recent years.[6]

CRS is a group of disorders characterized by inflammation of the mucosa of nose and paranasal sinuses for at least 12 weeks duration. In 1996, the American Academy of Otolaryngology–Head and Neck surgery multidisciplinary rhinosinusitis task force (RTF) defined adult rhinosinusitis diagnostic criteria. In 2003, the RTF definition was amended to require confirmatory radiographic or nasal endoscopic or physical examination findings in addition to suggestive history.[6] RTF has given a list of symptoms for diagnosing CRS. There are at least two major factors or one major factor with two or more minor factors: Major factors are (1) facial pain, (2) facial congestion, (3) nasal obstruction, (4) nasal discharge, (5) hyposmia/anosmia, (6) purulence in nasal cavity, and (7) fever. Minor factors are (1) headache, (2) fever, (3) halitosis, (4) fatigue, (5) dental pain, (6) cough, and (7) ear pain/pressure.

The anatomy of drainage revolves around the osteomeatal unit, which is not a single morphologic structure but a combination of the following structures: Uncinate process, ethmoid bulla, middle turbinate, infundibulum,

Table 3: Assessment of OMC obstruction MDCT versus ESS

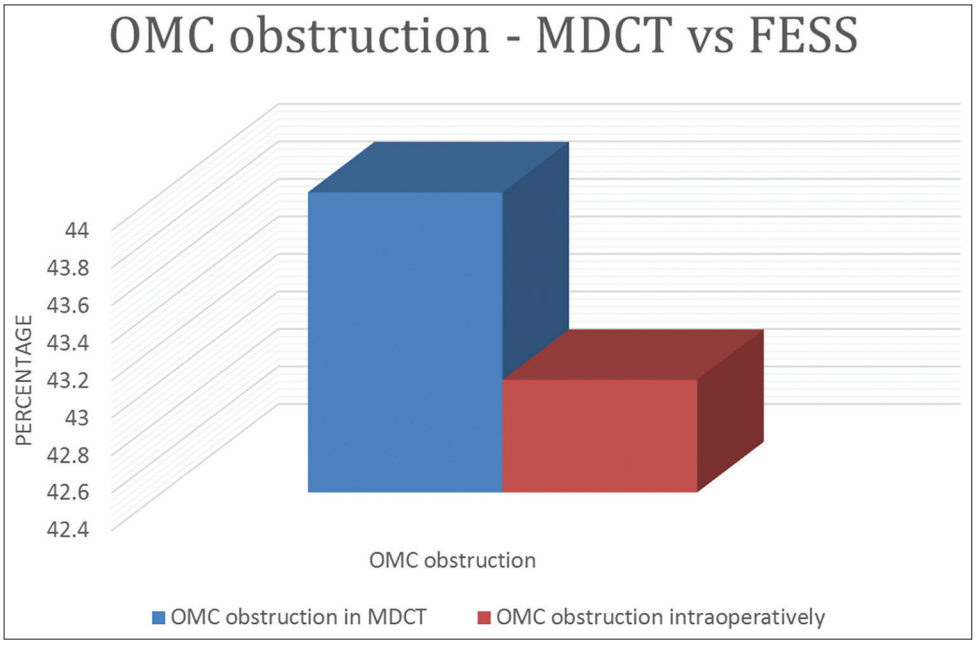
Status of OMC	MDCT	ESS
	n (%)	*n* (%)
OMC obstruction	44 (44.0)	43 (43.0)

MDCT: Multidetector-row Computed tomography, ESS: Endoscopic sinus surgery

Table 4: Correlation between preoperative MDCT scan and endoscopic sinus surgery findings in chronic sinusitis with regard to OMC obstruction

Status of OMC	Sensitivity	Specificity	PPV	NPV	Corelation	κ	Agreement	*P* value	Statistical significance
OMC obstruction	93.2	94.6	93.2	94.64	Excellent	0.878	Very good	< 0.01	Significant

*Sensitivity of - >90 is excellent correlation, >80 is good correlation, >70 is acceptable, >60 is poor correlation. †Kappa's value: 0.81–1.0 is very good agreement between CT scan and operative findings, 0.61–0.80 is good agreement, 0.41–0.60 is moderate agreement, 0.21–0.40 is fair agreement, <0.2 is poor agreement, CT: Computer tomography, MDCT: Multidetector-row Computed tomography, PPV: Positive predictive values, NPV: Negative predictive values



Graph 2: Percentage distribution of OMC obstruction detected by multidetector-row Computed tomography versus functional endoscopic sinus surgery

and hiatus semilunaris. According to Mackay and Lund, the osteomeatal complex acts as a drainage pathway for maxillary, anterior ethmoids, and frontal sinus. In several areas of OMC, two mucosal layers contact each other, thus increasing the likelihood of local impairment of mucociliary clearance.

The role of imaging is to document the disease extent, to answer questions regarding ambiguous vases, and to provide an accurate display of the anatomy of the sinonasal system. Now, CT has been the modality of choice for imaging evaluation of the morphology in this area. The introduction of MDCT has widened the range of applications of helical CT in clinical imaging, especially in the field of virtual imaging. With the help of MDCT, it is possible to obtain thin sections with improved Z-axis resolution, high-quality multiplanar resolutions, and volume rendered images. Volume acquisition makes it possible to retrospectively reconstruct overlapping images, thus producing high quality three-dimensional reconstruction. MDCT possesses the potential of radiation dose reduction by 20%; therefore, it should be the imaging method of choice in chronic sinusitis.[7]

CT has always been the gold standard for pre-operative evaluation. There is a high correlation between findings of CT examination and intraoperative endoscopic findings, but there are discrepancies also. In several studies, the findings that suggested sinus disease were intraoperatively seen polyps, purulent discharge, and edematous mucosa.[8] Till date, very few studies are there on the correlation between endoscopy and CT scan in the diagnosis of CRS on patients, but the detailed correlation of per-operative endoscopic findings and pre-operative CT scan findings is not much reported.

Our study was a prospective observational study aimed at a comparative evaluation of pre-operative MDCT findings and intraoperative endoscopic sinus surgery findings with regard to osteomeatal complex in patients with CRS.

The demographic data analysis of this study showed that 40% of the patients who underwent FESS for refractory CRS belongs to the age group 30–60 years. The mean age was 35.15 ± 13.48 years ranging from 18 to 81 years. The percentage of females (53%) was more than males (47%).

Majority of the study population presented with nasal obstruction (100%) which was present in all patients in this study group. It was followed by nasal discharge/purulence/discolored postnasal discharge (91%), cough (79%), headache and facial pain (73%), dental pain (64%), and facial congestion/fullness (63%). Less common symptoms were fatigue (16%), hyposmia (14%), halitosis (11%), ear pain/pressure/fullness (10%), and purulence on nasal cavity examination (5%). Maxillary sinus was found to be the most common sinus involved in MDCT in patients with CRS in our study.

In the present study, the most common anatomical variant in MDCT was agger nasi (72%), which are present in the area anterior and superior to the insertion of middle turbinate and its relationship on CT is essential for the diagnosis of chronic frontal sinusitis.

Its prevalence varies widely in studies by different authors such as Midilli *et al*., Gupta *et al*., and Kaygusuz *et al*. at 80.4%, 68.8%, and 64.6%, respectively.[9-11] Our study had similar results to Narendrakumar and Khojastepour *et al*. where the most common anatomical variant was agger nasi.[12,13] The sensitivity of MDCT was 100% for detecting agger nasi, and there was very good correlation between MDCT and FESS in our study ($\kappa = 1$, $P < 0.01$) which was similar to the previously conducted study by Devan *et al*. and Ravi *et al*.[14,15] with radiological imaging by CT.

The second most common anatomical variant detected in our study by MDCT was concha bullosa (95.3%) which is a pneumatized middle turbinate, which when large can cause blockage of middle meatus leading to sinusitis. This was similar to the study conducted by Bolger *et al*. where the incidence of CB in CRS was 53%.[16] The sensitivity of MDCT for detecting CB was 86.9% and there was a good correlation between MDCT and FESS in our study ($\kappa = 0.838$, $P < 0.01$), similar to previous studies by Prashant and Harugop and Ravi *et al*.[15,17] with radiological imaging by CT. Intraoperatively, the incidence of CB in our study was 61%. The decreased detection of CB by MDCT may be attributed to the presence of inflammatory exudates within the pneumatized CB.

Uncinate process variations were the third most common findings in our study with medial deviation of the uncinate process seen in 26% and lateral deviation of the uncinate process in 13%. Uncinate process is a key anatomical structure in the lateral wall of the nasal cavity; the medial deviation of which can make contact with middle meatus threatening its permeability and lateral deviation can cause narrowing of hiatus semilunaris and infundibulum. In a similar previous study conducted by Mamatha *et al*., the incidence of medially rotated uncinate process was 25% which is close to our study.[18] Laterally rotated uncinate showed varying incidence in previous studies. Fadda *et al*. and Krzeski *et al*. showed a presence of laterally rotated uncinate in 21.4% and 9.5%, respectively.[19,20] The sensitivity of MDCT in detecting uncinate process variations was 100%, and there was an excellent correlation between MDCT and FESS in our study ($\kappa=1$, $P < 0.01$)

which was similar to the previously conducted study by Devan *et al.*[14] with radiological imaging by CT.

Paradoxical middle turbinate is a reversal of normal outward concavity of middle turbinate and can cause attenuation of normal airflow dynamics. The prevalence of paradoxical middle turbinate by MDCT in this study was 13%. Previous studies by Pérez-piñas *et al.* and Khojastepour *et al.* showed a prevalence of 10% detected by CT[21,22] and Vineetha *et al.* showed a prevalence of 11% detected by CT.[23] The sensitivity of MDCT in detecting paradoxical middle turbinate was 100%, and there was very good correlation between MDCT and FESS in our study (κ=1, $P < 0.01$) which was similar to the previously conducted study by Prashant and Harugop with radiological imaging by CT.[17]

Haller's cell, also called infraorbital ethmoidal cells, can cause narrowing of maxillary ostium or infundibulum predisposing to recurrent maxillary sinusitis. In our study, the prevalence of Haller's cell was 9%. This was in comparison with the previously conducted study by Zinreich *et al.* where the prevalence was 10%.[24] The sensitivity of MDCT in detecting Haller's cell was 100%, and there was good correlation (κ = 0.695, $P < 0.01$) between MDCT and FESS in our study. Previous studies by Devan *et al.* showed poor correlation between CT and FESS and very good correlation between CT and FESS were found in studies conducted by Ravi *et al.*[14,15]

On analyzing the status of OMC, 44% of the study population showed obstructed OMC detected by MDCT, but only 43% showed actual obstruction intraoperatively. This variation in findings may be due to the presence of edematous mucosa or discharge that may be cleared off later. Our study also showed that MDCT had a sensitivity of 93.2% in detecting OMC obstruction and there was a very good correlation (κ = 0.878, $P < 0.01$) between pre-operative MDCT and intraoperative findings with regard to OMC obstruction. Previously conducted studies with routine CT showed poor to moderate correlation for the same findings. In studies conducted by Handanakere *et al.* and Prashant and Harugop, there was moderate correlation and in a study conducted by Kaku *et al.*, there was poor correlation between CT and intraoperative findings.[17,25,26] This results may be due to the superiority of MDCT compared to routine CT in the detection of this pathology.

The findings which we observed in our study points to the fact that pre-operative MDCT has a good correlation between the anatomical variants with regard to OMC which plays a pivotal role in CRS pathogenesis, and it has a very good correlation with regard to OMC obstruction which is a key factor related to the severity of CRS compared to intraoperative findings compared to previously conducted studies with routine CT. Going by the results of this study, it can be said that MDCT can be a better predictor of OMC related findings in patients with CRS and the necessity of unwanted surgery can be limited to a certain extent.

CONCLUSION

This was a prospective correlational descriptive clinical study conducted in 100 patients with diagnosed CRS refractory to medical treatment who had been advised FESS. Most patients were in third to sixth decades of their life, with a slightly more incidence in males (53%) compared to females (47%). The most common symptom with which they presented was nasal obstruction followed by nasal discharge/discolored postnasal discharge and cough. On evaluating the patients with MDCT PNS, the most common sinus involved was maxillary and anterior ethmoid sinus (93%) and least involved was sphenoid sinus (58%). The results of intraoperative findings regarding anatomic variants and OMC obstruction are more conclusive in the elucidation of final diagnosis than that obtained by MDCT PNS. However, MDCT was useful to visualize anatomic variants and the status of OMC preoperatively. MDCT shows increased sensitivity compared to routine CT in detecting OMC obstruction, and it had a very good correlation with intraoperative findings. There was an excellent correlation between MDCT and intraoperative findings in cases of all anatomic variants except concha bullosa. Concha bullosa showed a good correlation. In conclusion, MDCT can help clinicians to predict the OMC status pre-operatively and thereby guide FESS.

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Original Article

Oral Ferric Pyrophosphate Formulation Utilization Surveillance Study to Assess Clinical Impact on Hemoglobin levels: Maxiim-Hemoglobin Study

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Abstract

After hemorrhage, anemia is the most common cause of maternal mortality and leading cause of maternal morbidity in India. The prevalence rates of anemia in pregnancy in India is estimated to be >50%. Iron deficiency anemia (IDA) is the most common type of anemia in pregnancy in India, which I can be as high as 80–90%.

Aims and Objectives: The present survey was initiated in pursuit of analyzing the effectiveness and safety of oral ferric pyrophosphate (FPP) formulation given once to twice daily for treatment and prophylaxis of IDA in pregnancy.

Materials and Methods: This was a questionnaire-based retrospective survey. Each gynecologist was given this survey booklet containing questionnaire. Clinical response was assessed by measuring rise in mean hemoglobin (Hb) levels at baseline, week 4, and week 8, after giving oral FPP formulation for 8 weeks.

Results: A total of 60 gynecologists participated and completed the survey, which involved 1073 pregnant subjects and patients suffering from IDA (864 patients, i.e., 80%). Mean Hb level at baseline was found to be 8.98 g/dl, 10.03 at week 4, and 10.99 at week 8. Thus, rise of Hb from baseline to week 8 was found to be 2.01 g/dl. Adverse events were reported in only 10 patients (<0.09%), none requiring discontinuation of therapy. 98% of the participants agreed good acceptability of oral FPP formulation.

Conclusion: Findings of the present survey suggests that oral FPP formulation therapy can serve as potent choice of therapy for IDA in pregnancy, both therapeutically and prophylactically.

Key words: Ferric pyrophosphate, Gynecologists, Hemoglobin, Iron deficiency anemia, Oral ferric pyrophosphate formulation, Pregnancy, Survey

INTRODUCTION

Pregnancy is a unique experience in every women life. Unfortunately, pregnancy is engrossed with significant morbidity and mortality, especially in developing countries like India.[1] Anemia is one of the most common cause of maternal mortality and leading cause of maternal morbidity in India.[2] The estimated number of sufferers from anemia in pregnancy is around 2 million, on a global scale.[1] The prevalence rates of anemia in pregnancy in India are estimated to be >50%, as per the World Health Organization (WHO) and National Family Health Survey.[3,4]

Anemia in pregnancy is defined statistically as condition, characterized by decreased hemoglobin (Hb) which is less than two standard deviations of the median range of matched age, trimester of pregnancy in normal subjects.[5] Plethora of standard health and research organizations such as the WHO, Centre for Disease Control (CDC), and Indian Council of Medical Research (ICMR) has defined anemia in pregnancy as Hb <11 g/dl in all the three trimesters, except for CDC which has laid down cutoff for the second trimester as <10.5 and <11 for the rest and hematocrit <33%.[5-8] ICMR has further categorized anemia in pregnancy into mild, moderate, and severe categories with Hb 10–10.9, 7–10, and <7, respectively.[6]

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Iron deficiency anemia (IDA) is the most common type of anemia in pregnancy in India, which is estimated to be as high as 80–90%.[9-11] Pathophysiologically, IDA is characterized by depletion of iron stores in the body, which ultimately results in an absolute deficiency of iron in the body and tissues are deprived of iron. Biochemical parameters suggestive of IDA are derangements in serum levels of ferritin, erythrocyte protoporphyrin, transferrin saturation, and total iron-binding capacity.[12] IDA evolves through three stages:

- Stage 1 - reduction of iron stores
- Stage 2 - iron-deficient erythropoiesis
- Stage 3 - absolute depletion of iron stores/overt iron deficiency/IDA.[13,14]

The most common cause of IDA in pregnancy is nutritional deficiency, i.e., poor intake of iron in diet.[15] Although IDA is slow to develop in non-pregnant population, it develops faster in pregnancy since physiological hemodilution is usually present in pregnancy.[12] There are numerous evidences in literature that suggest linkage of IDA in pregnancy and increased rates of spontaneous abortion, prematurity, low birth weight, fetal growth retardation, and even fetal death in very severe cases.[16,17] It was found in a clinical study that perinatal mortality was increased 3 times when maternal Hb was <8 g/dl as compared to Hb level of 11 g/dl.[18] Therefore, numerous guidelines advocate iron supplementation in pregnancy and this has become a routine part clinical care of pregnant women, irrespective of the presence of IDA.[6,7]

Iron supplementation in pregnancy can be given orally and parenterally, but oral supplements are preferred over the later, although parenteral being more efficacious. This is due to better feasibility and patient compliance.[19,20] Plethora of oral iron salts is available for this purpose, which includes ferrous sulfate, ferrous fumarate, and ferric citrate.[21] Globally, ferrous sulfate is most commonly prescribed iron salt for prophylaxis and treatment of IDA in pregnancy.[22,23] Although efficacy of these conventional iron salts is well established, the gastrointestinal intolerance caused by them offsets their use. These adverse effects are comprised diarrhea, dyspepsia, nausea, vomiting, constipation, abdominal pain, and blackish discoloration of stools. Moreover, absorption of conventional iron salts is hampered by the presence of phytates, calcium, and tannins in the food by converting absorbable ferrous form to comparatively less absorbable ferric form through oxidation reaction.[24] In pursuit of overcoming these shortcomings, newer iron salts such as ferrous ascorbate, iron polymaltose complex, and ferric pyrophosphate were introduced,[25] of which ferric pyrophosphate is the recent one and has shown promising results in clinical studies.[26]

The present survey was initiated in pursuit of analyzing the effectiveness and safety of oral ferric pyrophosphate (FPP) formulation given once to twice daily in the treatment and prophylaxis of IDA in pregnancy. To the best of our knowledge, the present survey is the first of its kind to analyze the effectiveness and safety of FPP alone in pregnant women with large sample size.

MATERIALS AND METHODS

The present survey was conducted using a prevalidated questionnaire, which was structured to analyze the effectiveness and safety of FPP in the treatment and prophylaxis of IDA in pregnancy. Survey was of 10-month duration, from January 2018 to October 2018. Gynecologists involved in the treatment and prophylaxis of IDA in pregnancy were identified through "Scrip" intelligence database. Among these, 60 gynecologists were selected across four directional zones of the country to ensure uniform sampling. These gynecologists were selected on the grounds of maintaining complete patient records.

Each gynecologist was given the survey questionnaire in the form of survey booklet. At the end of survey period, these questionnaires booklets were analyzed, to assess the effectiveness and safety of oral FPP formulation in IDA of pregnancy.

Effectiveness Evaluation

Effectiveness evaluation was done by analyzing Hb levels at baseline, week 4, and week 8. Mean Hb was calculated for each visit and rise of Hb from baseline to week 4, week 4–8, and baseline to week 8 was calculated after giving FPP for 8 weeks.

Safety Evaluation

All the adverse events (AEs), mainly gastrointestinal intolerance, were analyzed for severity and their association with FPP, at each visit. The AE which occurred numerously in same patient was counted as one AE only.

Apart from this, patient acceptability of oral FPP was measured on a scale, where responses ranged from strongly agree to strongly disagree.

Statistical Analysis

Hb values were expressed as mean. Student's *t*-test was applied to compare these mean values at baseline, week 4, and week 8. $P < 0.05$ was set as cutoff for statistical significance [Figure 1].

RESULTS

Of a total of 1300 pregnant participants, 1073 were finally included for analysis, of which 864 (80%) had IDA. Mean

age of study participants was 28.6 years. Mean height and weight were 155.9 cm and 56 kg, respectively [Table 1].

The mean Hb at baseline was found to be 8.98 g/dl. This rose to 10.03 at the second visit/week 4 and 10.99 g/dl at the third visit, i.e., week 8 [Table 2].

On analyzing the rise in mean Hb, it was found that there was a rise of 1.05 g/dl in week 4 as compared to baseline, 0.96 in week 8 as compared to week 8, and 2.01 in week 8 as compared to baseline [Table 3 and Figure 2].

Only 10 participants of 1073 (<0.09%) reported AEs, which were mild and transient. None of the study participants discontinued FPP therapy. Bloating and constipation were most commonly reported, only in two patients each. Other AEs reported were mild belching, nausea, vomiting, and abdominal pain in one patient each [Table 4].

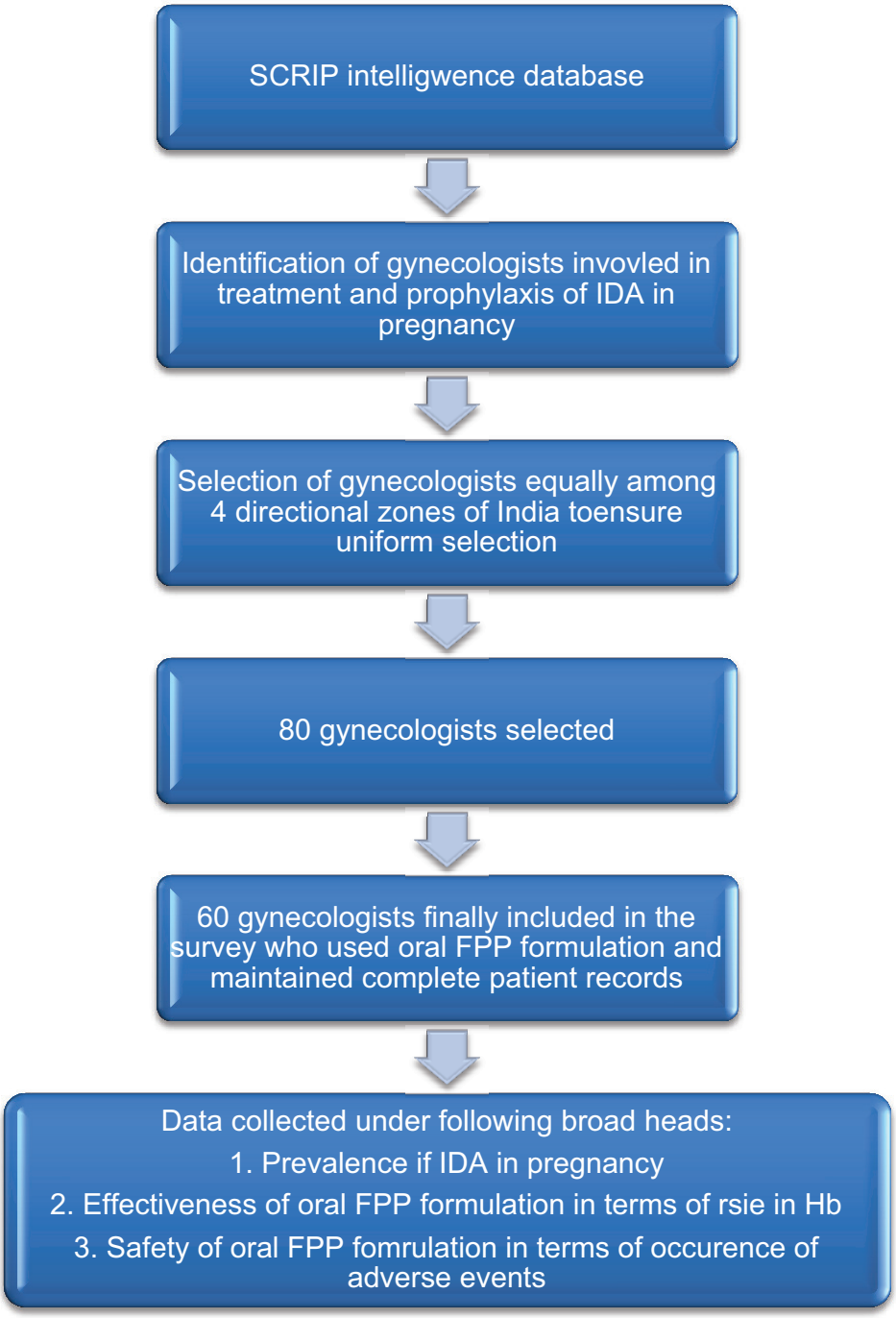

Figure 1: Methodology embraced for the present survey

On analyzing patient acceptability of oral FPP formulation, it was found that majority of the patients agreed that FPP showed good effectiveness in terms of the amelioration of clinical symptoms and tolerability; 1059 (99%) participants agreeing to this effect and only 16 participants disagreeing [Figure 3].

Table 1: General details of the study participants

Total number of participants	1073
IDA	864
Mean age	28.68
Mean height	155.93
Mean weight	56

IDA: Iron deficiency anemia

Table 2: Mean Hb at baseline and weeks 4 and 8

Visit	Mean Hb (g/dl)
Baseline	8.98
Week 4	10.03
Week 8	10.99

Hb: Hemoglobin

Table 3: Mean Hb at various time points during survey period

Time period	Rise in mean Hb	*P*-value
Baseline to week 4	1.05	<0.05
Week 4–8	0.96	<0.05
Baseline to week	2.01	<0.001

Hb: Hemoglobin

Table 4: AEs reported by study participants

Adverse event	Number of patient
Mild belching	1
Bloating	2
Constipation	2
Gastritis and nausea	1
Vomiting	1
Pain abdomen	1
Nausea	1
Had severe acidity, but after starting with antacid, compliance achieved	1

AEs: Adverse events

DISCUSSION

Anemia in pregnancy is one of the major contributors to maternal morbidity and mortality in India.[27] IDA is the most common anemia encountered in pregnancy.[9] IDA leads to plethora of maternal and fetal complications during and after pregnancy.[28,29] Iron supplements, preferably oral formulations, are used therapeutically and prophylactically for IDA in pregnancy. These iron supplements help to increase Hb levels in blood.[30]

In the present survey, IDA was found in 80% of the pregnant participants. Similar prevalence rate is reported in one study conducted by Narayanan and Bhargava *et al.*[31] There are numerous reasons for such high prevalence of IDA in pregnancy. Lack of optimal nutritional care in pregnancy is still a major issue in India.[32] Furthermore, poor patient compliance is somehow responsible for such high prevalence. This is due to the fact that, even if iron supplements are effective in ameliorating IDA in pregnancy, be it therapeutic or prophylactic use, their gastrointestinal adverse effects offset regular use by therapeutically or prophylactically. All these lead to poor patient compliance which ultimately leads to suboptimal protection against IDA in pregnancy.[33]

One of the most important parameters to assess the efficacy of iron supplements is rise in Hb. Rise in mean Hb in the present survey was 2.01 g/dl at the end of survey period. Singhal *et al.* in their clinical study compared efficacy and safety of various iron salts such as ferrous ascorbate, ferrous fumarate, and ferrous bisglycinate in pregnant patients suffering from IDA. They measured mean Hb at day 30 and day 60 and compared these to baseline values. Maximum rise in Hb was seen with ferrous ascorbate, which was 0.63 g/dl at day 30 and 1.13 g/dl at

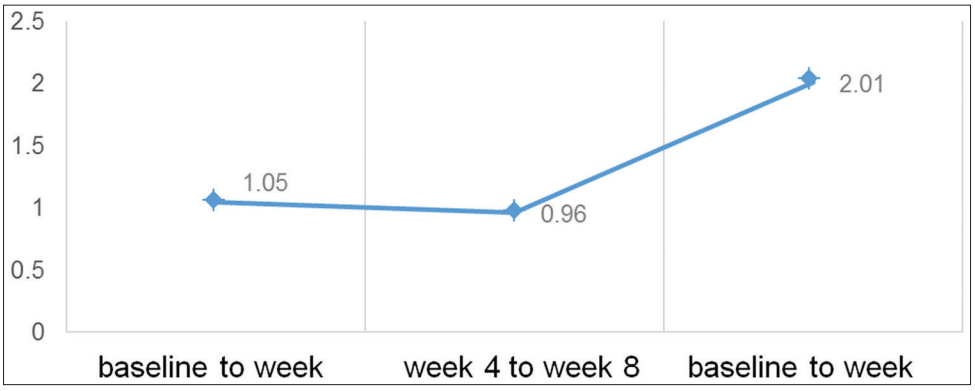

Figure 2: Rise in mean hemoglobin at various time points during the survey period

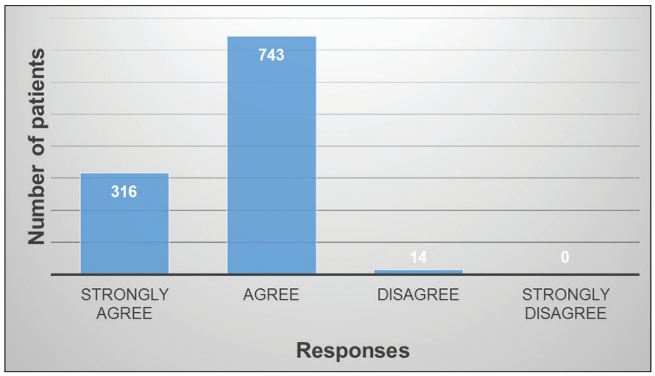

Figure 3: Patient acceptability response to oral ferric pyrophosphate

day 60.[25] Numerous studies have found good efficacy of various iron salts in increasing Hb and the average Hb rise reported with these salts at day 60 was found to be around 1.23 g/dl.[25,26] In a randomized, double-blinded clinical trial by Lagana *et al.*, efficacy and safety of FPP was analyzed in pregnant patients suffering from IDA. The rise in Hb obtained with the regular intake of FPP was somewhat less than that obtained with the present study.[26] Thus, rise in Hb obtained with oral FPP formulation in the present survey is way higher than other iron salts, as seen in various clinical studies.

This high rise in Hb with oral FPP formulation in the present survey might be attributed to the combination with other components as well. Folic acid and methylcobalamin in this formulation act as erythropoietic stimulants since they are involved in purine and thymidylate synthesis and thus help in maturation in erythroblasts.[34,35] Deficiency in these components results in apoptosis of erythroblasts and ultimately results in anemia due to inefficient erythropoiesis.[36] Vitamin C present in the oral FPP formulation helps in increasing the absorption of iron form the gut and it does so, by dual action - first, it curbs the materialization of unabsorbed iron compounds, and second, it increases the formation of ferrous form by reduction of ferric form, the earlier one being the preferred form for mucosal uptake in the intestinal cells.[37]

Reduced bioavailability is another major issue surrounding the use of oral iron supplements.[25] Moreover, Indian diet is rich in inhibitors of iron absorption in the gut (phytates, tannins, and calcium).[24] They inhibit the absorption of iron by converting ferrous to unabsorbable ferric form.[24] Moreover, this ferrous form participates in the Fenton reaction and leads to the formation of reactive free radicals, which ultimately results in oxidative damage.[38]

Various manufacturing technologies have been employed in pursuit of increasing the bioavailability of oral iron formulations. Of these, micronization, nanonization, and encapsulation of iron with liposomes have fetched significantly better bioavailability results.[38,39] It is well-known concept that smaller the particle size of drug, better is its absorption. Same principle is applied in nanonization technology, in which particle size of iron is reduced to nanoparticle size (10^{-9}) to aid its absorption in the gut, and was found to increase the bioavailability significantly in a randomized, double-blinded clinical trial on FPP.[39]

Similarly, liposomal encapsulation of iron offers some unique advantages over conventional iron formulations. Liposome-encapsulated iron follows different absorption fate as compared to conventional iron.[38] Since the structure and chemical composition of liposomes is almost similar to that of cell membrane, which allows liposome encapsulated iron to fuse with the cell membrane and enabling direct release of iron into the interior of the cells. It, thus, bypasses the usual protein-mediated iron transport which limits the absorption of iron. Thus, liposome encapsulation increases the absorption of iron which is reflected in a significant increase in Hb, hematocrit, erythrocyte iron, serum iron, and ferritin levels, as found in one study.[38]

Gastrointestinal intolerance-related adverse effects are one of the major setbacks to regular use of conventional iron formulations, which reduce the patient compliance.[30] These AEs were found in <0.09% of the total study participants in the present survey and that too were mild and transient, with none of the patients requiring discontinuation of FPP therapy. These findings are in corroboration with that of clinical trial done by Lagana *et al.* on micronized FPP in pregnant women with IDA.[26] Thus, findings of the present survey suggest that oral FPP formulation with nanonization and liposome encapsulation is effective and safe for treating IDA in pregnancy.

The current survey had certain limitations. First, given the design of the survey chances of bias cannot be ruled out. Second, head-to-head comparison with other iron salts should have been done. Finally, other indicators of IDA should have been evaluated, such as hematocrit, serum ferritin, and serum total iron binding capacity.

CONCLUSION

Oral FPP formulation therapy can serve as potent choice of therapy for IDA in pregnancy, both therapeutically and prophylactically. The oral FPP formulation in the present survey offered numerous advantages such as nanonization and liposomal encapsulation technologies to increase the absorption of FPP and presence of other erythropoietic components such as folic acid and methylcobalamin. Furthermore, the gastrointestinal AEs were very less, thus

making it an attractive choice of the treatment for IDA in pregnancy.

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Original Article

Association of Impacted Third Molars with Facial Growth Patterns among Adult Indian Patients - A Retrospective Study

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Abstract

Introduction: The third molar (3M) varies more than other molars in terms of shape, size, timing of eruption, and tendency toward impaction. Hence, studies need to be carried out to clarify the association of the various patterns of facial growth with mandibular 3M impaction.

Purpose: The purpose of this study is to relate the level of impaction of mandibular 3Ms and their inclinations to various patterns of facial growth among Indian patients.

Materials and Methods: A total of 207 lateral cephalograms and optic pathway gliomas (OPGs) of patients were obtained from NISSAN Radiological and Diagnostic Centre. The OPGs were analyzed by a single examiner as per: (1) Angulations (using Quek's analysis - beta angle, 2003). (2) Depth of 3Ms. The lateral cephalograms were assessed by a single examiner using: (1) Down's analysis. (2) Beta angle. (3)Jarabak's ratio. (4) Bjork's analysis.

The subjects were further classified into skeletal Class I, II, and III as well as into horizontal, vertical, and normal growth patterns. The final study data were subjected to a Pearson correlation test to check the association between the 3M impactions and various angles. The values found significant were coded into ordinate data and Kendall's Tau-B Test was done.

Results: Statistically, significant correlation was found between depth of impacted mandibular 3Ms and facial angle, Y-axis, cant of occlusion, angle of convexity, and gonial angle.

Conclusion: Greater incidence of 3Ms was found to be at position B and C in Class II patients as compared to Class I and III patients. Furthermore, patients showing vertical growth pattern were found to have increased percentage of mandibular 3M impactions.

Key words: Beta angle, Bjork's analysis, Down's analysis, Facial growth pattern, Jarabak's ratio, Lateral cephalogram, Third molar impactions, Third molar

INTRODUCTION

The term "impacted" originates from a Latin word "impactus" (wedged). The WHO defined an impacted tooth like the one that is unable to fully erupt in its normal functional occlusion/location by its expected age of eruption, because it is blocked by overlying soft tissue or bone or another tooth.

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The third molar (3M) varies more than other molars in terms of shape, size, timing of eruption, and tendency toward impaction.[1] There are many causes of 3M impactions such as inadequate spacing, reduced mandibular growth, inadequate mandibular length, and varied facial growth.

Björk found that failure of wisdom tooth in the lower arch to erupt completely was usually associated with lack of space in the alveolar arch between the second molar and the ascending ramus.[2,3] A short mandibular length is thought to be another etiologic factor in M3 impaction.

However, Kaplan did not find any significant difference in the mandibular length between subjects with erupted and impacted 3Ms.[4]

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Broadbent believed that when a 3M became impacted, it was due to an inability of the mandible to achieve its full growth potential.[5,6] Richardson has found that there was reduced amount of mandibular growth in 3M impactions cases.[7] Forsberg found that failure of eruption and degree of arch crowding were proportional.[2] Bjork showed that 3M impaction was not only associated with a reduced amount of growth but also with a downward as opposed to forward growth direction.[8] However, Legović *et al.* showed no significant difference between the position of mandibular M3 and the type of facial growth.

Due to these controversies, further studies need to be carried out to clarify the association of the various patterns of facial growth with mandibular 3M impaction.

Thus, the purpose of this study is to relate the level of impaction of mandibular 3Ms and their inclinations to various patterns of facial growth among Indian patients.

MATERIALS AND METHODS

Sample Selection

NISSAN Radiological and Diagnostic Center, Pune, was contacted, and 207 lateral cephalograms and optic pathway gliomas (OPGs) of patients were obtained after seeking permission from Dr. Akshay Shah.

Note: Only those patients were included in the study that had both OPGs and lateral cephalograms taken at the same time.

Exclusion Criteria

The following criteria were excluded from the study:

- Unclear OPGs and lateral cephalograms.
- OPGs of patients undergoing or who have previously undergone orthodontic treatment.
- OPGs showing lesions or fractures or artifacts.
- OPGs of patients showing multiple missing teeth especially posteriors.
- Presence of mandibular M3s with less than two-thirds of root formation.
- History of medical problems with a potential effect on facial growth.

Requisite Permissions and Duration of Study

This study was conducted between May 2018 and September 2018 after receiving approval from the Institutional Ethics Committee (Reference No.: YMTDC/1125/2018).

Sample Collection and Analysis

- Panoramic radiographs were taken for each patient with the upper and lower incisors in an edge-to-edge relationship using the XTROPAN 2000 unit at 65 kVp, 10 mA, and 17.6 s.

The OPGs were analyzed by a single examiner as follows:

- Angulations (using Quek's analysis - beta angle, 2003).

The angle formed between the intersection of the long axis of second and 3M was measured in degrees and categorized as follows as shown in Figure 1:

- Depth of 3Ms.

As per the relationship between the occlusal surface of the impacted 3M with that of the adjoining second molar, the depth of the 3M is classified as as shown in Figure 2:

- Position A: Highest position of 3M is at or above the occlusal plane.
- Position B: Highest position of 3M is below the occlusal plane but above the cervical line of the adjacent 2nd molar.
- Position C: Highest position of 3M is below the cervical line of the adjacent 2nd molar.

Lateral cephalograms were taken for each patient in centric occlusion with the lips in repose and the Frankfort plane horizontal, according to the natural head position, using a XTROPAN 2000 X-ray unit at 65 kVp, 10 mA, and 14.2 s exposure.

A pilot study was conducted (using Down's analysis and Bjork's analysis) to compare between OneCeph app and manual method of cephalometrics tracing. The pilot study data were subjected to the *t*-test in which we found that there was statistically no significant difference between the two methods. Considering the ease of use of this app over manual tracing, OneCeph app was used to record the various angles on the lateral cephalogram.

The lateral cephalograms were then assessed by a single examiner using:

- Down's analysis (Angle of convexity, facial angle, AB plane angle, mandibular plane angle, Y-axis, and cant of occlusal plane),
- Beta angle,
- Jarabak's ratio and
- Bjork's analysis (Saddle angle, articular angle and gonial angle - upper and lower, and sum of angles) as shown in Figure 3.

The subjects were further classified into skeletal Class I, II, and III as well as into horizontal, vertical, and normal growth patterns as shown in Table 1.

(The values in Table 1 have been taken from standard Indian textbooks showing average values of the respective angles as seen in the average Indian population).

Table 1: Classification of sample into Class I, II & III, and vertical, horizontal & normal growth patterns as per various cephalometric analysis

Angles	Class I	Class II	Class III
Facial angle	82–95	<82	>95
Angle of convexity	−8.5–10	>10	<−8.5
AB plane angle	−9–0	<−9	>0
Y-axis	53–66	>66	<53
Cant of occlusion	1.5–14	>14	<1.5
Saddle angle	118–128	>128	<118
Articular angle	137–149	>149	<137
Beta angle	27–35	<27	>35
Angles	**Normal**	**Vertical**	**Horizontal**
Mandibular plane angle	17–28	>28	<17
Y-axis	53–66	>66	<53
Jarabak's ratio	62–65	<62	>65
Gonial angle	123–137	>137	<123
Upper	52–55	>55	<52
Lower	70–75	<70	>75
Sum of angles	396	>396	<396

Tables 2: Classification of mandibular 3Ms as per depth and type of impaction

Tooth number	Mandibular *n* (%)
Tooth status	
Present	390 (94.2)
Absent	24 (5.8)
Total	414 (100)
Depth	
A (1)	199 (48.1)
B (2)	154 (37.2)
C (3)	37 (8.9)
Total	390 (94.2)
Type of impaction	
Vertical	149 (36)
Mesioangular	211 (51)
Horizontal	21 (5.1)
Distoangular	8 (1.9)
Others	1 (0.2)
Total	390 (94.2)

The final study data were compiled in an Excel sheet, and Pearson correlation test was used to check the association between the 3M impactions and various angles enlisted above. The values thus found significant were further coded into ordinate data and Kendall's Tau-B Test was done.

RESULTS

After analyzing 207 OPGs, we found 390 mandibular molars suitable to include in our study [Table 2].

Out of the 390 mandibular 3Ms evaluated, 199 (48.1%) were found to be at Position A followed by 154 (37.2%) at Position B and 37 (8.9%) at Position C as shown in Figure 4.

Tables 3: Standard Deviations of values obtained on evaluation of lateral cephalogram analysis

Type of angles	Mean±SD	Minimum	Maximum
Angel of convexity	6.40±7.06	−14	24
Facial angle	84.37±5.250	72	99
AB plane angle	8.64±11.030	−7	96
Mandibular plane angle	25.09±6.744	7	41
Y axis	63.53±5.086	49	76
Cant of occlusion	12.07±10.585	−5	106
Jaraback's ratio	70.74±6.214	57	89
Saddle angle	121.22±6.001	104	141
Articular angle	143.87±7.048	126	167
Gonial angle	122.41±6.96	103	140
Upper	52.33±6.8	41	159
Lower	73.64±45.62	55	704
Beta angle	30.99±5.96	16	47
Sum of angles	387.49±6.882	369	405

SD: Standard deviation

Tables 4: Correlation of various cephalometric analysis with depth and type of mandibular 3M impaction using Pearsons Correlation Test

Angles	Depth		Angle code/type of impaction	
	r value	*P* value	*r* value	*P* value
Angel of convexity	0.099	0.025*	0.026	0.301
Facial angle	0.217	0.001*	0.027	0.299
AB plane angle	0.030	0.278	0.003	0.479
Mandibular plane angle	0.074	0.071	−0.040	0.214
Y-axis	0.138	0.003*	−0.047	0.180
Cant of occlusion	0.128	0.006*	0.034	0.250
Jaraback's ration	0.007	0.446	0.043	0.198
Saddle angle	−0.044	0.194	0.011	0.413
Articular angle	−0.069	0.087	−0.031	0.273
Gonial angle	0.086	0.045*	0.017	0.367
Upper	0.033	0.256	0.022	0.331
Lower	0.005	0.461	0.046	0.181
Beta angle	−0.064	0.103	0.002	0.482
Sum of angle	0.036	0.238	0.070	0.083

About 149 (36%) of the mandibular 3Ms were found to be vertically impacted, 211 (51%) showed mesioangular impactions, 21 (5.1%) were horizontally impacted, and 8 (1.9%) showed distoangular impactions as shown in Figure 5.

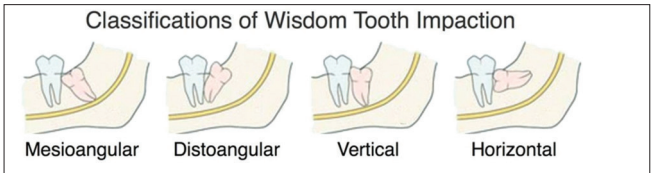
The lateral cephalograms of the same patients were evaluated and the results thus obtained are shown in Table 3.

After applying the Pearson correlation test, the results thus obtained are shown in Table 4.

As shown in Table 4, statistically significant correlation was found between depth of impacted mandibular 3Ms and facial angle ($P = 0.001$), Y-axis ($P = 0.003$), cant of occlusion ($P = 0.006$), angle of convexity ($P = 0.025$), and Gonial angle ($P = 0.045$).

Tables 5: Further results obtained on applying Kendall Tau-B test

Angles	Position A *n* (%)	Position B *n* (%)	Position C *n* (%)	Total *n* (%)	Approx T[b] value	*P* value
Facial angle						
Class I	148 (58.9)	89 (35.2)	16 (6.3)	253 (61.3)	7.065	0.001*
Class II	48 (37.2)	61 (47.3)	20 (15.5)	129 (31.2)		
Class III	3 (37.5)	4 (50)	1 (12.5)	8 (1.9)		
Cant of occlusion						
Class I	143 (55.4)	95 (36.8)	20 (7.8)	258 (62.5)	5.544	0.001*
Class II	49 (42.2)	52 (44.8)	15 (12.9)	116 (28.1)		
Class III	7 (43.8)	7 (43.8)	2 (12.5)	16 (3.9)		
Angle of convexity						
Class I	147 (54.2)	102 (37.6)	22 (8.1)	271 (65.6)	5.111	0.001*
Class II	47 (42.7)	48 (43.6)	15 (13.6)	110 (26.6)		
Class III	5 (55.6)	4 (44.4)	0	9 (2.2)		
Gonial angle						
Normal	104 (54.7)	73 (38.4)	13 (6.8)	190 (46)	4.810	0.001
Vertical	1 (33.3)	2 (66.7)	0	3 (0.7)		
Horizontal	94 47.7)	79 (40.1)	24 (12.2)	197 (47.7)		
Y-axis						
Normal	150 (55.4)	101 (37.3)	20 (7.4)	271 (65.6)	5.718	0.001*
Vertical	45 (39.8)	51 (45.1)	17 (15)	113 (27.4)		
Horizontal	4 (66.7)	2 (33.3)	0	6 (1.5)		



Type	Angulation
Vertical impaction	(−10° to 10°)
Mesioangular impaction	(11° to 79°)
Horizontal impaction	(80° to 100°)
Distoangular impaction	(−79° to−11°)
Others	(−111° to−80°)

Figure 1: Classifications of wisdom tooth impaction

No significant correlation was found between the angle of impaction and the various cephalometric angles.

The values thus found significant were further coded into ordinate data and Kendall's Tau-B Test was done and the results obtained are shown in Table 5.

Facial angle (formed by the intersection of nasion pogonion plane and Frankfort horizontal [FH] plane) gives us an indication of anterior-posterior positioning of the mandible. Thus, its value increases in skeletal Class III and decreases in skeletal Class II cases.

When we segregated our sample into Class I, II, and III based on the facial angle and compared it with the position of mandibular 3M, we found that:

- In Class I patients, 58.9% of 3Ms were found to be at Position A, 35.2% at Position B, and 6.3% at Position C.
- In Class II patients, 37.2% of 3Ms were found to be at Position A, 47.3% at Position B, and 15.5% at Position C.
- In Class III patients, 37.5% of 3Ms were found to be at Position A, 50% at Position B, and 12.5% at Position C.

Cant of occlusion (formed between the occlusal plane and FH plane) gives us a measure of the slope of the occlusal plane relative to the FH plane.

When we segregated our sample into Class I, II, and III based on Cant of occlusion and compared it with the position of mandibular 3M, we found that:

- In Class I patients, 55.4% of 3Ms were found to be at position A, 36.8% at position B, and 7.8% at position C.
- In Class II patients, 42.2% of 3Ms were found to be at Position A, 44.8% at Position B, and 12.9% at Position C.
- In Class III patients, 43.8% of 3Ms were found to be at Position A, 43.8% at Position B, and 12.5% at Position C.

The angle of convexity is formed by the intersection of a line from nasion to point A and point A to pogonion. A positive angle suggests a prominent maxillary denture base relative to the mandible. A decreased or negative angle suggests a prognathic profile.

When we segregated our sample into Class I, II, and III based on the angle of convexity and compared it with the position of mandibular 3M, we found that:

- In Class I patients, 54.2% of 3Ms were found to be at Position A, 37.6% at Position B, and 8.1% at Position C.

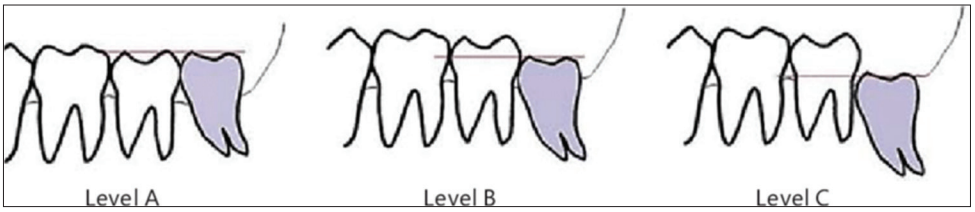


Figure 2: Classification of 3M impactions as per depth

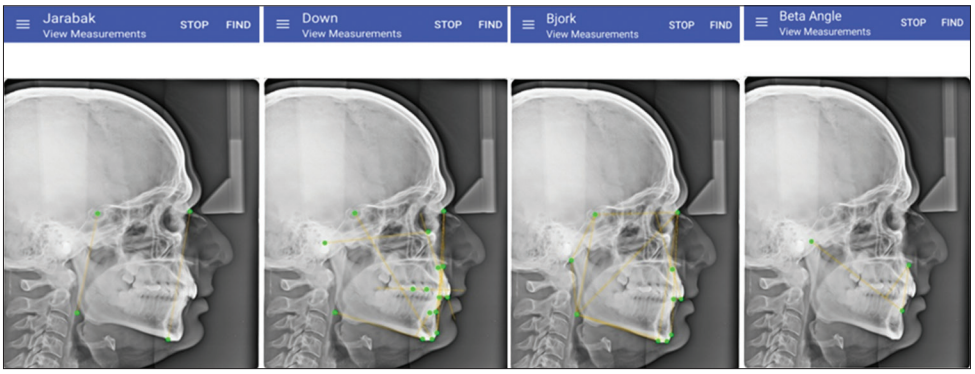


Figure 3: Analysis done on lateral cephalograms using OneCeph application

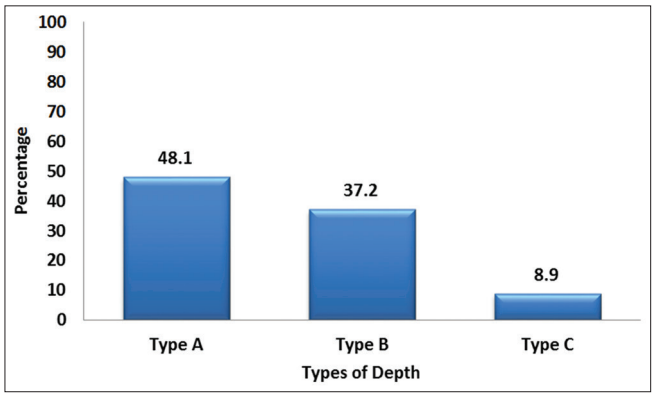


Figure 4: Percentage distribution of type of depth

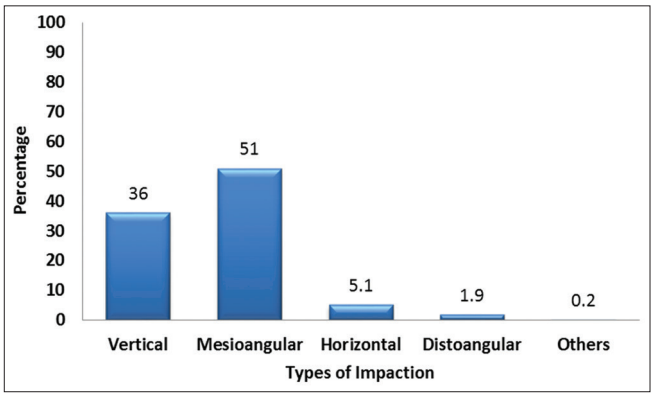


Figure 5: Percentage distribution of types of impaction

- In Class II patients, 42.7% of 3Ms were found to be at Position A, 43.6% at Position B, and 13.6% at Position C.
- In Class III patients, 55.6% of 3Ms were found to be at Position A, 44.4% at Position B, and 0% at Position C.

Y-axis (angle formed by joining sella-gnathion line with the FH plane.) indicates the growth pattern of the individual. Increased value indicated greater vertical growth of mandible whereas decreased angle indicates greater horizontal growth of the mandible.

When we segregated our sample into normal, vertical and horizontal growth pattern based on Y-axis and compared it with the position of mandibular 3M, we found that:

- In patients with a normal growth pattern, 55.4% of 3Ms were found to be at Position A, 37.3% at Position, and 7.4% at Position C.
- In patients with vertical growth pattern 39.8% of 3Ms were found to be at Position A, 45.1% at Position B, and 15% at Position C.
- In patients with horizontal growth pattern, 66.7 % of 3Ms were found to be at Position A, 33.3% at Position B, and 0% at Position C.

Gonial angle is formed by joining the lines between articulare and gonion and gonion and menton. Small angle indicates a horizontal growth pattern whereas a larger angle indicates vertical growth pattern.

When we segregated our sample into normal, vertical and horizontal growth pattern based on the gonial angle and compared it with the position of mandibular 3M, we found that:

- In patients with a normal growth pattern, 54.7% of 3Ms were found to be at Position A, 38.4% at Position B, and 6.8% at Position C.

- In patients with vertical growth pattern, 33.3% of 3Ms were found to be at Position A, 66.7% at Position B, and 130% at Position C.
- In patients with horizontal growth pattern, 47.7 % of 3Ms were found to be at Position A, 40.1% at Position B, and 12.2% at Position C.

Thus, a greater incidence of 3Ms was found to be at Position B and C (i.e., partially or completely impacted) in Class II patients as compared to Class I and III patients.

Furthermore, patients showing vertical growth pattern were found to have an increased percentage of mandibular 3M impactions (i.e., 3M at Position B and C).

DISCUSSION

Mandibular 3M impactions are multifactorial in its occurrence in which facial growth seems to play an essential role.

Our study shows the rate of mandibular 3M impactions to be 46.1% which was similar to the findings of [9] Pushappreet who found the rate of mandibular 3M impactions to be 54% with the right side more frequently involved. However, lesser rates of impaction were reported by[10] Andreason (18–32%) and[11] Dachi and Howell (17.5%) whereas a higher rates of 3M impactions were reported by[12] Sapkota *et al.* (63.77%) and[13] Vilela and Vitoi (60%).

Our study shows mesioangular impactions as the most prevalent (51%) which is similar to the findings of[14] Quek *et al.*,[15] Sandhu and Kaur,[16] Ventä *et al.*, and[17] Padhye *et al.*

Higher prevalence of mesioangular impaction might be related to the developmental position of its primordial germ, found high up in the mandibular ramus with its occlusal surface slanting mesially or sometimes, horizontally, and the developing crown then moves in response to postural change in the mandible induced by growth.[9,18] Cessation of jaw growth before complete uprighting of the crown will most likely trap the developing tooth in a mesioangular position.

Our study shows a greater incidence of impacted mandibular 3Ms in patients with Angle's Class 2 (Skeletal) malocclusion.

Similar results were reported by Richardson who found that skeletal Class II dental base relationship with a shorter, narrower, and more acute-angled mandible was found in association in impacted 3Ms, compared with erupted teeth.[6]

Yassaei *et al.* found that in Class I and II malocclusion, most teeth were erupted to Level B. In Class III malocclusion, the level of most teeth was at the level of the occlusal plane of M2.[19] This might be due to the fact that skeletal Class III patients have a prognathic mandible leading to more availability of space for an eruption of M3 as compared to skeletal Class I and II patients.

However, Abu Alhaija found an increased rate of mandibular 3M impactions in skeletal Class III patients.[20]

An explanation for this opposite result could be the way in which the malocclusion has been determined. Abu Alhaiji used only ANB Angle for classification of malocclusion which gives a relative position of the upper jaw in relation to the lower jaw but does not specify the relative position of the jaws to the rest of the facial skeleton. Thus, multiple angles should be recorded for more accuracy of results.

Our study also reported that patients showing vertical growth pattern have a greater incidence of mandibular 3Ms at Position B and C, i.e., partially or completely impacted as compared to patients with normal and horizontal growth patterns.

Breik and Grubor also found an increased rate of mandibular impactions in cases with facial axis 87>, i.e., dolichofacial (long face) profile.[3]

Sapkota *et al.* found the highest occurrence of 3M impactions in dolichocephalic type and least in brachycephalic type.[12]

However, no significant relationship was found between the angular position of 3Ms and the facial type in this study.[19] Yassaei *et al.* were also unable to find any such correlation between the angle of 3M and the malocclusion.

The minimum age of patients selected in this study was 20 years (Mean age: 25.76 years). The reason is that the growth of the jaws is usually completed by the age of 18 years. Thus, at the age of 20 years, it is possible to distinguish whether a 3M is in the normal eruptive process or will remain impacted in the jaw.

Limitations of this study include small sample size and sample type. Since growth is a multi-factorial phenomenon, a wide variety of factors can influence it and hence a larger sample size would give more accurate results. The sample consists of pre-orthodontic records of orthodontic patients. These patients are more likely to show malocclusion and crowding causing the greater occurrence of 3M impactions as compared to the general population.

CONCLUSION

Within the limitations of our study, our hypothesis that the rate of impaction in vertical growers is more than the patients with normal or horizontal growth patterns holds true. This is so because the space required for the eruption of lower 3Ms seems to be provided in patients having a horizontal or normal growth pattern compared to those having a vertical growth pattern.

Our study also concludes that the rate of mandibular 3M impaction is greater in patients showing skeletal Class II relation as compared to those showing skeletal Class I and Class III relations.

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Original Article

Outcome of Type 1 Tympanoplasty with Cartilage-perichondrium Graft in Comparison with Temporalis Fascia

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Abstract

OBJECTIVE: To compared the outcome of Type 1 tympanoplasty with cartilage-perichondrium graft in comparison with temporalis fascia graft in terms of post-operative graft take-up and hearing results.

MATERIALS AND METHODS: A prospective observational study among 80 patients between 15 and 60 years of age satisfying the inclusion criteria with complaints of ear discharge and hearing loss due to COM - mucosal type was conducted. Patients were grouped in two groups of 40 patients each. Group A patients underwent Type 1 tympanoplasty with temporalis fascia and Group B with cartilage-perichondrium graft. Patients were followed up for graft uptake, hearing improvement and rate of failure are compared for both the grafts. Graft uptake was assessed at the end of the 1st month, 3rd month, and 6th month, and hearing was assessed at the end of the 6th month with pure tone audiometry.

RESULTS: Patients with temporalis fascia graft showed a take-up rate of 80% and cartilage-perichondrium graft of 92.5% by 6 months. Among the fascia group, graft failure was seen in 20% (8). One patient had failed take-up of graft and four patients showed reperforation. In cartilage group, three patients showed failure of take-up of graft during the 1st month. No patient had reperforation or retraction. Air-bone gap in fascia group showed a closure to 10 dB in 17.5% (7). In the cartilage group, 10 dB in 25% (10 patient s). In our short-term follow-up of 6 months, we found that cartilage-perichondrial graft reduces the chance of reperforation and retraction even with variation in middle ear pressure due to eustachian tube catarrh. It gives good take-up rate and comparable hearing result as that of the fascia graft. It does not affect the sound conduction when thinned out to appropriate thickness. It is available from the same surgical field and in sufficient quantity for the closure of the TM defect. Cartilage-perichondrium graft for Type 1 tympanoplasty could be a successful replacement for temporalis fascia giving good result with neotympanum.

Key words: Cartilage perichondrium, Neotympanum, Temporalis fascia, Type 1 tympanoplasty

INTRODUCTION

Chronic otitis media (COM) is a result of the previous episode of acute otitis media, otitis media with effusion, or trauma to the tympanic membrane (TM). This causes a permanent defect of the pars tensa which leads to recurrent infection and ear discharge. Eventually, these patients may develop hearing loss and further complications. These patients can be managed surgically by doing a tympanoplasty. Type I tympanoplasty or myringoplasty repairs the perforation of TM alone. The goal of Type I tympanoplasty includes the prevention of recurrent infection of middle ear from external pathogens and restoration of the vibratory area of TM which improves hearing. The closure of perforation is achieved using different autologous graft materials. The commonly used graft materials are temporalis fascia, perichondrium, cartilage, fascia lata, vein, and fat. Among the various options available otologists prefer to use temporalis fascia or perichondrium as it gives a good healing, sufficient

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quantity of graft, good tensile strength, and acoustic property similar to that of normal TM. Unfortunately, fascia grafts are found to succumb to infections and significant pressure gradient during the post-operative period. This can be avoided in certain cases using a cartilage-perichondrial graft.

Cartilage perichondrium is being successfully used in the reconstruction of TM in the past. The rigid nature of cartilage is thought to interfere with the sound transmission properties, even though it effectively prevents retraction and reperforation.

Aim

The aim of this study was as follows:

1. To study the take-up of cartilage perichondrium and temporalis fascia as graft material in Type 1 tympanoplasty.
2. To assess the post-operative retraction or reperforation of neotympanum in using cartilage perichondrium and temporalis fascia graft.

MATERIALS AND METHODS

During the study period from September 2015 to February 2017, 80 patients with complaints of ear discharge due to the mucosal type of COM with conductive hearing loss were recruited for the study. The patients of age 18–70 years were divided into two groups after a thorough clinical examination. The two groups are fascia group and cartilage group of 40 patients each. Fascia group underwent Type 1 tympanoplasty with temporalis fascia. Cartilage group underwent Type 1 tympanoplasty with tragal or conchal cartilage along with perichondrium. Grafts were placed using underlay technique in all patients.

A thorough clinical examination of ear nose and throat was done. An otoscopic examination was done to record the site and size of perforation. Size of perforation was classified into small, medium, or large depending on the involvement of one quadrant, two quadrants, and three or more than three quadrants, respectively [Figure 1]. All findings were confirmed with examination of the ear under microscope. Hearing status was assessed with pure-tone average (PTA) and hearing threshold at 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz, and air-bone gap observed. Hearing loss was graded into mild (25–35 dB), mild-moderate (36–45 dB), and moderate-severe (45–60 dB) [Figure 2]. Patients with other comorbidities such as Type 2 diabetes mellitus and hypertension were managed medically. Diagnostic nasal endoscopy and indirect laryngoscopy were done to rule out any pathology and foci of infection. X-ray of paranasal sinuses was taken to rule out coexistent sinusitis. Those patients with foci of infection in the upper respiratory tract which influence the patency of eustachian tube were treated. Cortical mastoidectomy was done in patients with sclerotic mastoid and ensured a patent aditus to facilitate middle ear aeration. Wet ears were made dry by giving systemic antibiotics according to culture and sensitivity, local antibiotic ear drops, and asking the patient to observe.

Routine pre-operative investigations included examination under microscope, ear swab culture and sensitivity, pure-tone audiometry, X-ray mastoids, diagnostic nasal endoscopy, Video laryngoscopy, X-ray paranasal sinuses, chest X-ray and ECG, routine blood investigations, random blood sugar, and renal function tests.

All patients were operated under general anesthesia. Patients were nil per oral from 10 PM. Ear was prepared by shaving 2 cm above and behind the ear. After intubation, patient was put in reverse Trendelenburg position with a head ring. The head of the patient is turned to opposite side so that the operating ear is facing upward. A folded towel is placed below the face on the opposite side for support. Pinna preauricular area and postauricular area are painted with betadine and draped.

Both postaural and transcanal approaches were used. Most of the ears were operated using Carl Zeiss operating microscope. Some cases were done using 0-degree endoscope for transcanal approach.

Graft Harvesting

Cartilage Perichondrium

The cartilage-perichondrium graft is harvested either from tragal cartilage or conchal cartilage. The tragus is injected with a local anesthesia. An incision along the free edge of tragus is made and the subcutaneous tissue is dissected to the lateral border of the cartilage and it is perichondrium. It is then harvested with it is attached perichondrium excess on one side. The donor site is then closed.

If the graft is from conchal cartilage, it is harvested by putting an anterior/posterior incision with preservation of it is associated perichondrium. The cartilage-perichondrium graft is prepared by elevating the perichondrium from one side of the cartilage while maintaining it is attachment on the other side of the cartilage.

The temporalis fascia graft is harvested through an extended postaural incision or through a separate 2 cm incision in the temporal region of scalp after infiltrating with 2% lignocaine and 1:100,000 adrenalin. The graft is then dried over a bowl of hot water [Figure 3].

Tympanoplasty procedure

The edges of the perforation are freshened. The tympanomeatal flap is elevated from 6 O'clock to 12 O'clock position. Ossicular intactness and mobility are confirmed. After putting antibiotic steroid soaked gel foam in the middle ear, the graft is placed medial to the handle of malleus and carefully tucked below the perforation. The tympanomeatal flap is repositioned. The final graft position is checked and readjusted if required. The external auditory canal is filled with antibiotic steroid soaked gel foam to stabilize the graft. A small ear pack soaked with antibiotic is kept in the ear canal. Incision is closed and mastoid dressing given [Figure 4].

When the graft is cartilage perichondrium, it is placed over the gel foam with the perichondrial side facing medially. Tympanomeatal flap is repositioned over it.

A cortical mastoidectomy is done in cases with a sclerotic mastoid and aditus patency is ensured. It facilitates aeration of middle ear and aids in the proper healing of graft.

All patients were given a mastoid dressing.

All patients were kept in post-operative intensive care unit for 24 h. Patients were kept nil per oral for 4 h postoperatively. IV fluids, IV antibiotics, and IV analgesics were given. Post-operative complications such as facial nerve weakness/palsy, soakage of mastoid dressing, vertigo, and nystagmus were observed. Mastoid dressing changed on the 1st post-operative day.

Patients were discharged on the 3rd post-operative day. Antibiotic, analgesic, decongestants, and antihistamines will be given for 1 week. Steroid nasal spray and mast cell stabilizers were continued in those patients with nasal allergy. Patients were advised not to cough, strain, or sneeze and keep ears dry. All patients were instructed to avoid air travel and swimming for 1 month.

Postaural suture removal was done on the 7th post-operative day. All patients were called for regular follow-up. The gel foam in the external auditory canal was not disturbed for 3 weeks. Antibiotic ear drops were started to facilitate dissolution of gel foam and to promote healing. On the 4th week, status of the graft was observed with otoscope. The same was done after 3 months and 6 months. PTA was done by the 6th month to assess the hearing.

All patients were followed up at regular intervals at the end of the 1st month, 3rd month, and 6th month after surgical procedure. By the end of 1 month, ear is observed for the status of the graft with otoscope alone. Any residual gel foam is cleared by gentle suctioning. By the end of the 3rd month, a healed neomembrane can be seen in case of a successful uptake of graft.

The graft take-up and gain in hearing are considered as the success of the surgery. The graft take-up was assessed by otoscopic examination. The surgery is considered as not successful in case of the failure of graft take-up, reperforation of the neomembrane, or graft retraction.

RESULTS

Among the 80 patients who underwent Type 1 tympanoplasty by disease eradication, 40 were repaired with temporalis fascia and 40 patients with cartilage perichondrium. These patients were followed up regularly for 6 months postoperatively.

The success of tympanoplasty was assessed by graft take-up and hearing improvement. Patients were followed up at 1 month, 3 months, and 6 months. The graft take-up was assessed by the end of 1 month, 3 months, and 6 months with otoscopic examination. A healed graft is considered to have a good take-up. Any residual perforation, retraction, or reperforation of graft are considered as a failure.

During the 1st month, graft take-up was seen in 97.5% (39) in fascia group and 92.5% (37) in cartilage group. The graft failure was seen only in one patient in fascia group due to upper respiratory tract infection which led to ear discharge and graft destruction. In cartilage group, three patients showed graft failure. Two of them had severe nasal allergy as they failed to use steroid nasal spray and antihistamine. One patient had infection during the 1st post-operative month, which led to graft rejection, [Table 1 and Graph 1].

By the 3rd month, in fascia group, take-up rate came down to 92.5% (37). Three patients showed graft failure. Two of them had reperforation following allergic rhinitis and upper respiratory tract infection. In cartilage group, the take-up rate remained constant at the end of the 3rd month, [Table 2 and Graph 2].

At the 6th month, follow-up was done to assess the neotympanum formation and hearing level. Graft was assessed using otoendoscopy and hearing assessment was done using pure-tone audiometry. In fascia group, by the end of the 6th month, success rate came down to 80% (32), which means graft failure has occurred in five patients and graft retraction in three patients. In the cartilage group, the success rate is remained same, i.e., 92.5%. Three patients showed graft failure in the 1st month and no patient had graft retraction, reperforation, or medialization, [Table 4 and Graph 4].

DISCUSSION

COM is an inflammatory process in the middle ear space that results in long term, or more often, permanent changes in the TM including atelectasis, dimeric membrane, perforation, tympanosclerosis, retraction pocket development, or cholesteatoma. Ossicular involvement is variable. COM results from long-term eustachian tube dysfunction with poorly aerated middle ear space, recurrent episodes of acute otitis media, persistent middle ear infection, or other chronic inflammations. COM is classified as active, inactive, and inactive with frequent reactivation.[1]

Inactive COM with perforation is a permanent defect of the TM without any ongoing inflammatory process or infection in the middle ear or mastoid. The TM has been ruptured in the past as part of the previous acute or chronic inflammation. The site of perforation can be the pars flaccida or pars tensa of the TM and can be marginal, central, subtotal, or total. Pathologically, there will be no inflammation of the mucosa of the middle ear space or mucosa, but the TM is perforated. The perforation can be surrounded by healthy residual TM, tympanosclerosis, a dimeric membrane, or thick scar. Sometimes, the perforation may extend onto the fibrous annulus. The lamina propria of the TM thickens at the periphery of the perforation due to fibrous tissue proliferation. The mucocutaneous junction is at the edge of the perforation and the epithelial cells migrate medially through the perforation or may stop at the edge. The presence of an epithelial lining within the middle ear space, if not removed before closure of the membrane perforation results in iatrogenic cholesteatoma.

Perforation can be in pars tensa or pars flaccida. Perforation in the pars tensa is called as central perforation. Perforation

Table 1: Percentage distribution of the post-operative result at 1 month

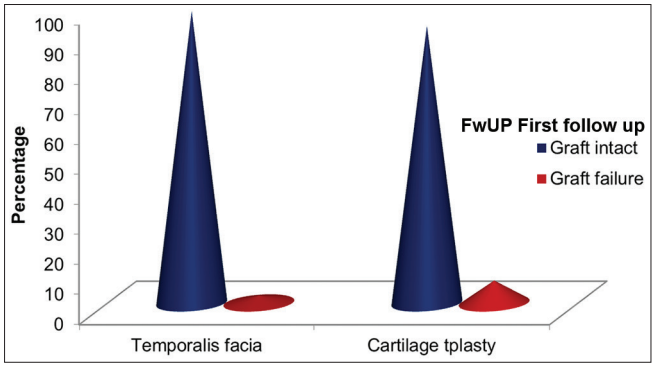
FwUP First follow-up	Temporalis fascia		Cartilage tympanoplasty		Total	
	n (%)		*n* (%)		*n* (%)	
Graft intact	39	97.5	37	92.5	76	95
Graft failure	1	2.5	3	7.5	4	5
Total	40	100	40	100	80	100

Table 2: Percentage distribution of the post-operative results at the 3rd month

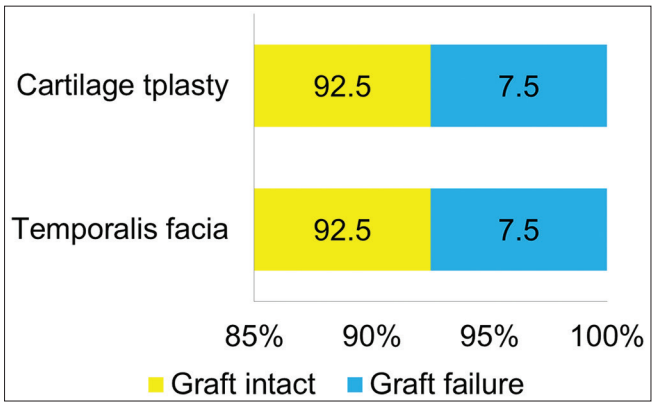
FwUP 3rd month	Temporalis fascia		Cartilage tympanoplasty		Total	
	n (%)		*n* (%)		*n* (%)	
Graft intact	37	92.5	37	92.5	74	92.5
Graft failure	3	7.5	3	7.5	6	7.5
Total	40	100.0	40	100.0	80	100.0

Table 3: Percentage distribution of the follow-up result at the 6th month

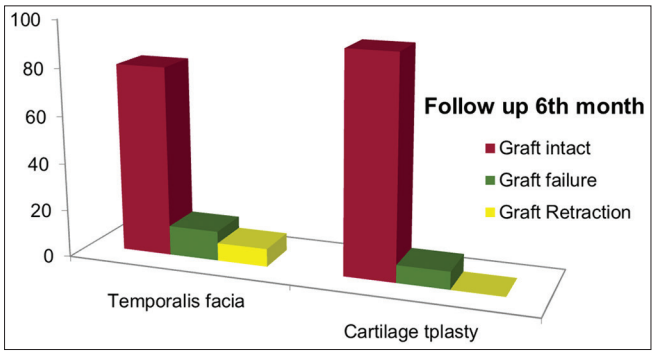
FwUP 6th month	Temporalis fascia		Cartilage tympanoplasty		Total	
	n (%)		*n* (%)		*n* (%)	
Graft intact	32	80	37	92.5	69	86.3
Graft failure	5	12.5	3	7.5	8	10
Graft retraction	3	7.5	0	0	3	3.8
Total	40	100	40	100	80	100



Graph 1: Percentage distribution of the post-operative result after 1 month



Graph 2: Percentage distribution of follow-up results at the 3rd month



Graph 3: Percentage distribution of follow-up result at the 6th month

can involve different quadrants of the TM. Anterior and posterior perforations are seen anterior and posterior to the handle of malleus, respectively. Inferior perforation is seen inferior to the handle of malleus. Subtotal perforations are very large perforation of pars tensa reaching up to the annulus of pars tensa. Marginal perforations are perforations which destroy the annulus and reach the sulcus tympanicus. It may be posterosuperior, anterior, inferior, and total perforation.

Frequent flare-ups can occur in an inactive ear. Each episode of reactivation or flare-ups can occur even without any triggering factor such as water entry or any upper respiratory tract infection in the presence of subclinical inflammation. Treatment of this subclinical infection is essential before undergoing TM closure. Without the treatment of this subclinical inflammatory process, failure of the surgical procedure can occur.[2]

The two goals of tympanoplasty are to achieve a dry ear after eradicating middle ear disease and improve hearing mechanism by the closure of TM with graft and ossicular reconstruction. The success of the surgery is determined by the graft take-up and hearing improvement. For the success of surgery, it should be planned according to the condition of each ear. Benign central perforations, with or without cholesteatoma, previous tympanoplasty failure, mucosal diseases, poor eustachian tube function, and erosions of ossicular chain are the different entities to be considered. Benign perforation with minimal ossicular changes is expected to obtain 93–97% chance for graft take-up and an 85–90% gain in hearing is within 20 dB of bone level.[3,4]

Indications of Tympanoplasty

Tympanic membrane perforation associated with hearing loss with or without middle ear pathology like tympanosclerosis, small retraction pockets and cholesteatomas.

Absolute Contraindication

1. Poor general health.
2. Malignant tumors of outer or middle ear.
3. Uncontrolled cholesteatoma.
4. Unusual infections like malignant otitis externa.
5. Complications of COM - meningitis, brain abscess, or lateral sinus thrombosis.
6. Only or significantly hearing ear to avoid the risk of irreversible sensorineural hearing loss.

Relative Contraindication

1. Eustachian tube dysfunction.
2. Smoking.[5]

A non-functioning eustachian tube is difficult to assess. Smoking is considered to have a negative impact on the success of the surgery. It is associated with 3-fold rise in long-term graft failure.[6,7] Elderly patients with relatively good general condition can be taken up for surgery without any significant risk. In children, it is delayed until 8–10 years if there is no bilateral TM perforation with significant conductive hearing loss or cholesteatoma.

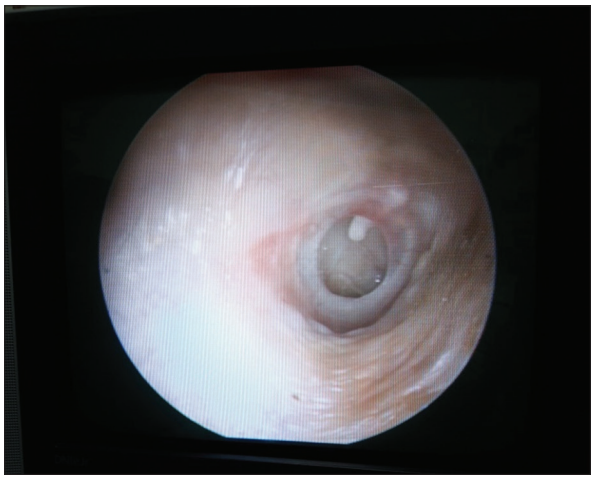


Figure 1: Otoendoscopic view of a large central perforation

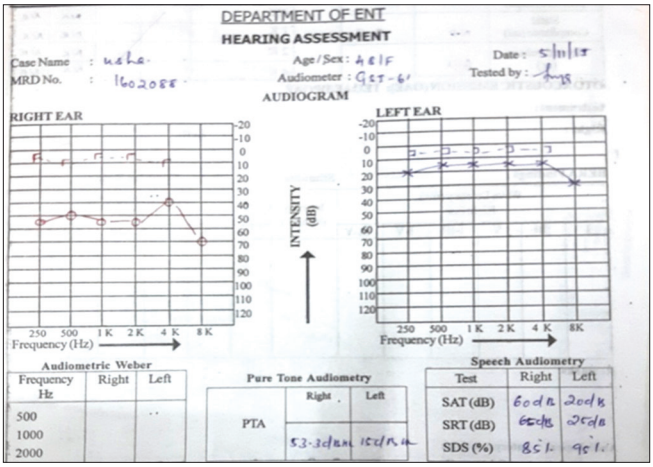


Figure 2: Pre-operative pure-tone average

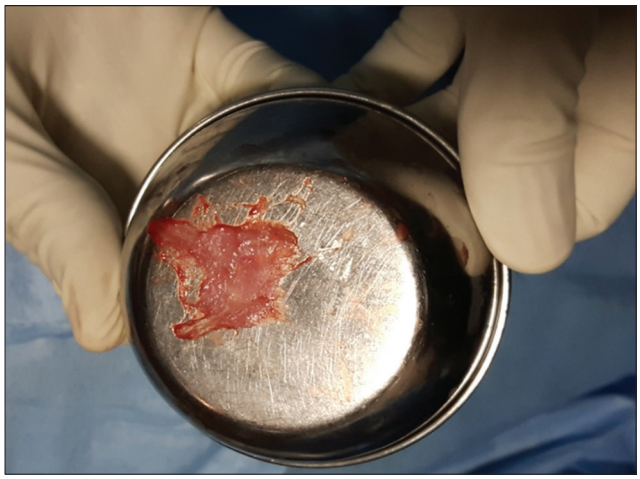


Figure 3: Temporalis fascia harvested

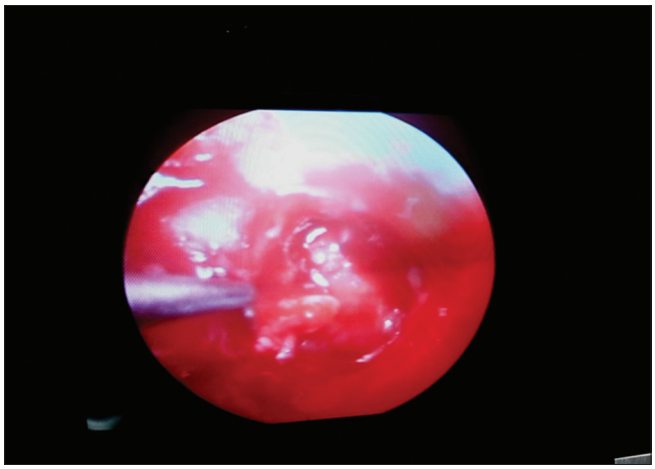


Figure 4: Graft placed using underlay technique

The aim of our study was to compare the uptake in cartilage perichondrium and temporalis fascia as graft material in Type 1 tympanoplasty using underlay technique. 80 cases of the mucosal type of COM with pure conductive hearing loss and intact ossicular chain were taken up for the study. 40 patients were subjected to Type 1 tympanoplasty with temporalis fascia and 40 patients with cartilage perichondrium by underlay technique with or without cortical mastoidectomy depending on the cellularity of mastoid.

The success of tympanoplasty was assessed by graft take-up and hearing improvement. Patients were followed up at 1 month, 3 months, and 6 months. The graft take-up was assessed by the end of 1 month, 3 months, and 6 months with otoscopic examination. A healed graft is considered to have a good take-up. Any residual perforation, retraction, or reperforation of graft are considered as a failure.

During the 1st month, graft take-up was seen in 97.5% (39) in fascia group and 92.5% (37) in cartilage group. The graft failure was seen only in one patient in fascia group due to upper respiratory tract infection which led to ear discharge and graft destruction. In cartilage group, three patients showed graft failure. Two of them had severe nasal allergy as they failed to use steroid nasal spray and antihistamine. One patient had infection during the 1st post-operative month, which led to graft rejection.

By the 3rd month, in fascia group, take-up rate came down to 92.5% (37). Three patients showed graft failure. Two of them had reperforation following allergic rhinitis and upper respiratory tract infection. In cartilage group, the take-up rate remained constant at the end of the 3rd month.

At the 6th month, follow-up was done to assess the neotympanum formation. Graft was assessed using otoendoscopy. In fascia group, by the end of the 6th month, success rate came down to 80% (32), which means graft failure has occurred in five patients and graft retraction in three patients. In the cartilage group, the success rate remained same, i.e., 92.5%. Three patients showed graft failure in the 1st month and no patient had graft retraction, reperforation, or medialization.

Several literatures are available regarding the study of different graft material. In a study conducted by Gibb and Chang *et al.* in 365 patients who underwent Type 1 tympanoplasty using temporalis fascia showed a take-up of 87.5%.[8] Another study conducted by Dabholkar *et al.*[9] in 50 patients showed 84% of take-up by temporalis fascia and 80% with tragal perichondrium. In a study conducted by Onal *et al.*,[10] in 2011, among 80 patients showed a success rate of 65.9% in fascia group and 92.3% in cartilage group. Our study showed almost similar result with the cartilage group. A study with palisade cartilage graft by Kazikdas *et al.*[11] found a 95.7% graft take-up when compared with a 75% take-up with temporalis fascia graft.

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Original Article

Evaluation of the Efficacy of Tamsulosin and Deflazacort versus Tamsulosin Alone in Expulsion of Lower Ureteric Stones in a Tertiary Center

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Abstract

Introduction: Urolithiasis is a very common problem present. About 70% of all ureteric stones are found in the lower third of ureter. Many factors affect the modality of treatment such as setup available, type, size of stone and expertise of the surgeon. Extracorporeal shock wave lithotripsy and ureteroscopy and removal of stone are very effective, but they require the help of anesthetist. Ureter is to be stented, and the stent has to be removed later on. They are very costly and not without complications. Many pharmacological agents have been used for the expulsion of ureteric stones, for example, diclofenac, alkalizers, ketorolac, nifedipine, deflazacort, prazosin, silodosin, and tamsulosin.

Materials and Methods: This prospective observational study was conducted in the Surgery Department at SGT Medical College. A total of 100 patients of distal ureteric stones of sizes 4–10 mm were taken in this study, divided into two groups of 50 patients each. Group I patients were given tamsulosin 0.4 mg and deflazacort 30 mg once in a day, Group II patients were given tamsulosin 0.4 mg once in a day. Treatment was for 10 days.

Results: In Group I, the stones were expelled in 38 (76%) patients, while in Group II, 26 (52%) patients passed stones. This is statistically significant with $P = 0.038$. The median time for stone expulsion was 3 days in Group I and 11 days in Group II with $P = 0.032$.

Conclusion: We have evaluated that medical expulsive therapy using tamsulosin alone is also effective and can be used in patients where steroids are contraindicated, but by adding deflazacort, it becomes very effective for management of distal ureteral calculi.

Key words: Deflazacort, Diclofenac, Expulsion, Pain, Symptoms, Tamsulosin, Urolithiasis

INTRODUCTION

Urolithiasis is a very common problem, present in almost in all geographical areas. It is present in all cultural and racial groups. It has been found out that the risk of urolithiasis is about 12% in the developed world and about 22% in developing countries.[1] Most common age affected is 15–45 years. Males are involved more commonly than females.[2] Urolithiasis is a great burden on the society.

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A ureteric stone is one that has passed from the kidney into the ureter. The stone is formed by deposition of small grains of solid material in kidney. About 70% of all ureteric stones are found in the lower third of ureter.[3] A stone passing down the ureter often causes intermittent attacks of ureteric colic. The waves of agonizing loin pain are typically to the groin, external genitalia, and the anterior surface of the thigh. As the stone enters the bladder, the pain can be referred to the tip of the penis.[4] There are many ways for the treatment of lower ureteric calculi. Many factors affect the modality of treatment such as setup available, type, size of stone and expertise of surgeon. Extracorporeal shock wave lithotripsy and ureteroscopy and removal of stone are very effective, but they require the help of anesthetist. The ureter is to be stented, and the stent has to be removed later on. They are very costly and not without complications. Many pharmacological agents

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have been used for the expulsion of ureteric stones, for example, diclofenac, indomethacin, floroglucine, alkalizers, ketorolac, nifedipine, progesterone, deflazacort, prazosin, alfuzosin, silodosin, and tamsulosin.[5-7]

MATERIALS AND METHODS

This prospective observational study was conducted in the Department of General Surgery at SGT Medical College, SGT University, Budhera, Gurugram, Haryana, India, from July 2017 to November 2018. A total of 100 patients coming to emergency or surgery outpatient department (OPD) complaining of colicky abdominal pain and diagnosed, distal ureteric stones of sizes 4–10 mm were taken in this study. Those patients having stones, of size >10 mm, bilateral stones, impaired kidney functions, urethral stricture, severe hydronephrosis, liver disease, and patients on beta-blockers and patients with pregnancy were excluded from this study. An informed consent, telling the patient and attendant(s) in detail about the nature of research study, was taken. A detailed history with details of pains and other symptoms was taken. Investigations included Hb, BT, CT, complete examination of urine, blood urea, serum creatinine, plain X-ray abdomen and ultrasonography of kidney, and ureter and urinary bladder region were done. For the relief of pain, injection diclofenac sodium 75 mg intramuscularly was given. Once the patient got relief of pain, the patient was sent home. Patients were advised to repeat this injection if pain recurred. Subsequently, patients were advised to attend OPD. 100 patients considered for the study were divided into two groups of 50 patients each, alternatively. Group I (study group) patients were given tamsulosin 0.4 mg once in a day and deflazacort 30 mg once in a day and Group II (controlled group) patients were given tamsulosin 0.4 mg once in a day. Treatment was carried on for 10 days. Patients were asked to note and tell if they passed the stone. Patients were reviewed after 2 weeks and 4 weeks. During follow-ups, X-ray and ultrasonography of kidney, and ureter and urinary bladder regions were done. Liver function tests and kidney function tests were done in all patients to see for any side effects. It was noted that how many times patients had pain, how much analgesics were required. All patients were asked to pass urine through a sieve to note the passage of the stone. Patients were asked in detail about side effects such as dizziness, hypotension, retrograde ejaculation, nasal congestion, nausea, vomiting, diarrhea, constipation and headache.

Study Design

This was a prospective observational study.

Selection of Subjects (Cases)

A total of 100 patients were studied. Informed consent was taken for examination.

Ethical Considerations

The study was started after taking approval from the Institutional Ethics Committee for Research on Human Subjects. Throughout the study, ethical considerations were followed strictly. Confidentiality was ensured. The data were collected, and entries were made, and analysis was carried out using statistical SPSS version 23 software. The analysis was studied using a Chi-square test.

RESULTS

The prospective observational study was performed in the Surgery Department in SGT Medical College, SGT University, Budhera, Gurugram, Haryana, over a period of 1 year and 5 months from July 2017 to November 2018. A total of 100 patients were studied. Informed consent was taken for examination. A detailed history with details of pains and other symptoms was taken. Investigations included Hb, BT, CT, complete examination of urine, blood urea, serum creatinine, plain X-ray abdomen and ultrasonography of kidney, and ureter and urinary bladder region were done. For the relief of pain, injection diclofenac sodium 75 mg intramuscularly was given. Once the patient got relief of pain, the patient was sent home. Patients were advised to repeat this injection if pain recurred. Subsequently, patients were advised to attend OPD. 100 patients considered for the study were divided into two groups of 50 patients each, alternatively. Group I (study group) patients were given tamsulosin 0.4 mg once in a day and deflazacort 30 mg once in a day and Group II (controlled group) patients were given tamsulosin 0.4 mg once in a day. Treatment was carried on for 10 days. Patients were asked to note and tell if they passed the stone.

There were no significant differences among both the groups so far as age (Table 1), sex (Table 2), location of stone (Table 3), and size of stone (Table 4) are considered. All the patients had colicky abdomen pain. Mostly 84% in Group I and 76% in Group II, had pain radiating to groin,

Table 1: Mean age

Characteristic	Group I	Group II	*P* value
Mean age	33.6	35.7	0.508

Table 2: Sex

Characteristic	Group I	Group II	*P* value
Sex			
Male	38	41	0.572
Female	12	9	

external genitalia, and the anterior surface of the thigh. Burning micturition, nausea, vomiting, and urgency were present in some patients. Gross hematuria was reported in 2 patients in each Group I and Group II patients (Table 5). Median stone size was 5.8 mm in Group I and 6.3 mm in Group II (Figures 1-3 showing stones of different sizes). Hydroureter was noted in 11 (22%) patients in Group I and 13 (26%) patients in Group II (Table 6). In Group I, the mean number of pain episode was 0.42±0.45 and in Group II the value was 0.57±0.64 (Table 7), which is also not statistically significant. It is clear that the numbers of pain episodes in Group I were lower than that in Group II. However, the numbers of pain episodes were almost similar in men and women. In Group I, 18 (36%) patients did not require any analgesics after the first dose, 22 (44%) patients required a second dose, in 8 (16%) patients third dose was required, and in 2 patients, >3 doses were required. In Group II, the respective figures were 14 (28%), 24 (48%), 9 (18%), and 3 (6%) (Table 8). In Group I, the stones were

Table 3: Stone location

Characteristic	Group I	Group II	*P* value
Stone location			
Right	32	29	0.572
Left	18	21	

Table 4: Median size of stone

Characteristic	Group I	Group II	*P* value
Median size of the stone in mm	5.6	6.1	0.609

Table 5: Symptoms

Symptoms	Group I	Group II	Total
Pain	50	50	100 (100%)
Radiation of pain	42	38	80 (80%)
Nausea	13	15	28 (28%)
Burning of micturition	7	6	13 (13%)
Urgency	6	8	14 (14%)
Hematuria	2	2	4 (4%)

Table 6: Incidence of back pressure changes

Groups	Hydroureter (%)	Hydronephrosis
Group I	11 (22)	Nil
Group II	13 (26)	Nil

Table 7: Incidence of mean pain episode after starting the treatment

Characteristics	Group I	Group II	*P* value
Mean pain episodes	0.42±0.45	0.57±0.64	0.023

Table 8: Amount of diclofenac used

Amount of diclofenac (in mg)	Group I (%)	Group II (%)
0	18 (36)	14 (28)
150	22 (44)	24 (48)
225	8 (16)	9 (18)
>225	2 (4)	3 (6)

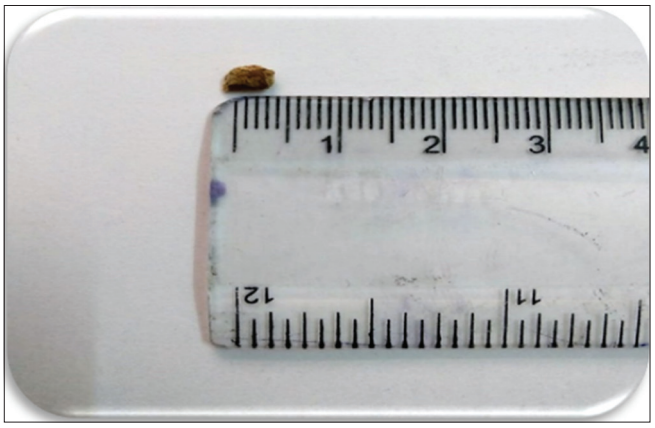

Figure 1: Stone size 3 mm

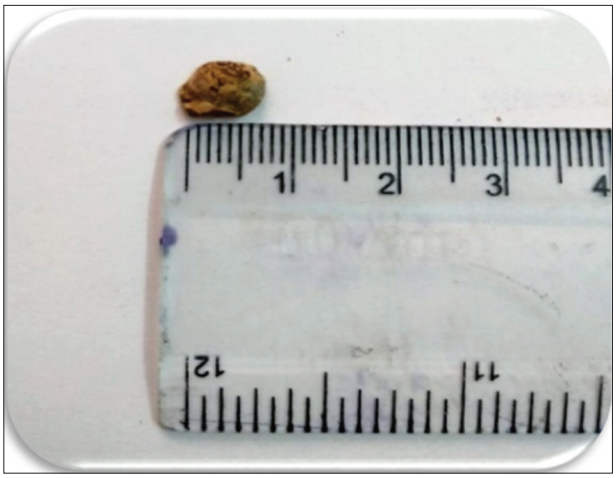

Figure 2: Stone size 7 mm

Figure 3: Stone size 8 mm

expelled in 38 (76%) patients while in Group II, 26 (52%) patients passed stones (Table 9). This is statistically significant with a p value of 0.038 (Table 9). The median time for stone expulsion was 3 days in Group I and 11 days in Group II with $P = 0.032$ (Table 10). So far as side effects are concerned, in Group I, we found retrograde ejaculation in 3 (6%) patients, nausea 6 (12%) patients, dizziness in 4 (8%) patients, headache in 7 (14%) patients, vomiting in 5 (10%) patients, constipation 6 (12%) patients, nasal congestion in 2 (4%) patients, and diarrhea in 1 (2%) patients. In Group II, we found retrograde ejaculation in 2 (4%) patients, nausea 4 (8%) patients, dizziness in 5 (10%) patients, headache in 4 (8%) patients, vomiting in 3 (6%) patients, constipation 0 (0%) patients, nasal congestion in 3 (6%) patients, and diarrhoea in 1 (2%) patients (Table 11). However, the side effects were not significant and therapy was not suspended.

DISCUSSION

We all know that ureteroscopy and removal of stone is the best treatment for the ureteral stone, but this demands anesthesia and stenting, hence there high cost involved with this procedure.[8] When we come across a symptomatic distal ureteric calculus suitable for expulsion, we are in search of proper pharmacological agent. We are in search of a proper pharmacological agent. The pharmacological agent usually acts by reducing the edema of the ureter and maintaining the tonicity of the ureter.[9] As we know the fact that a ureteric stone causes edema of the ureter and a steroid has anti-inflammatory action. Hence, it is very clear that if steroid is added, the chances of the expulsion of stone are greatly increased. Various studies have shown that α_1-blockers (tamsulosin along with deflazacort is very effective therapy for the expulsion of stones).[10-13] This study was conducted on 100 patients divided into two groups of 50 patients each, alternatively. Group I (study group) patients were given tamsulosin 0.4 mg once in a day and deflazacort 30 mg once in a day. Group 2 (controlled group) patients were given tamsulosin 0.4 mg once in a day. Treatment was carried on for 10 days. We selected tamsulosin because it is antagonist to alpha -1A and alpha -1D receptors present in the distal ureteral tract in high concentrations. Deflazacort was selected due to its antiedemic effects. I is also very well tolerated and the side effects also less.[14,15] The duration of therapy was 10 days only to avoid the side effects of long-term corticosteroid therapy. Further, as per the study of Malin Jr., *et al.*,[13] it was reported the efficacy of the corticosteroid therapy is more in 1st few days.

In this study first, we found the results of the expulsion of stones by excluding deflazacort. We have found that even without deflazacort the medical expulsive therapy using tamsulosin is also effective and can be used in patients where corticosteroid is contraindicated. However, the results are excellent with the combination therapy of tamsulosin and deflazacort.

So far as side effects are concerned, in Group I, we found retrograde ejaculation in 3 (6%) patients, nausea 6 (12%) patients, dizziness in 4 (8%) patients, headache in 7 (14%) patients, vomiting in 5 (10%) patients, constipation 6 (12%) patients, nasal congestion in 2 (4%) patients, and diarrhea in 1 (2%) patients. In Group II, we found retrograde ejaculation in 2 (4%) patients, nausea 4 (8%) patients, dizziness in 5 (10%) patients, headache in 4 (8%) patients, vomiting in 3 (6%) patients, constipation 0 (0%) patients, nasal congestion in 3 (6%) patients, and diarrhea in 1 (2%) patients. However, the side effects were not significant and therapy was not suspended.

Table 9: Expulsion rate

Characteristic	Group I	Group II	*P* value
Expulsion rate	76%	52%	0.038

Table 10: Median time of expulsion

Characteristic	Group I	Group II	*P* value
Median time of expulsion in hours	72	132	0.043

Table 11: Side effects of therapy

Side effects	Group I (%)	Group II (%)
Retrograde ejaculation	3 (6)	2 (4)
Nausea	6 (12)	4 (8)
Dizziness	4 (8)	5 (10)
Headache	7 (14)	4 (8)
Vomiting	5 (10)	3 (6)
Constipation	6 (12)	0 (0)
Nasal congestion	2 (4)	3 (6)
Diarrhea	1 (2)	1 (2)

CONCLUSION

We have evaluated that medical expulsive therapy using tamsulosin alone is also effective and can be used in patients where steroids are contraindicated, but by adding deflazacort, it becomes very effective for the management of distal ureteral calculi. Expenditure is very less. Patients can do his routine work with this therapy. Side effects are insignificant.

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Original article

Efficacy of Early N-Acetylcysteine in Rat Killer Paste Poisoning

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Abstract

Introduction: Rat killer paste (yellow phosphorous) is one of the most common forms of poisoning in South India. It causes hepatotoxicity. No specific antidote has been found. Recently, N-acetylcysteine is used as supportive therapy in many cases of acute liver failure.

Aim: This study aims to evaluate the effectiveness of early N-acetylcysteine in preventing the rat killer paste poisoning.

Methods: Patients who ingested rat killer paste poison and age >12 years were included in the study. Patients having jaundice, liver disease, and age <12 years were excluded from the study.

Results: Among 30 patients studied, five patients died, seven patients developed hepatitis, one patient developed acute kidney injury with hepatitis, and one patient developed hyponatremia.

Conclusion: Early initiation of N-acetylcysteine had a significant impact in reducing mortality.

Key words: Acute hepatic failure, N-acetylcysteine, Rat killer paste

INTRODUCTION

Rat killer paste poisoning is one of the causes of acute liver failure.[1] Rat killer (Ratol) paste contains yellow phosphorus. White phosphorous with its impurities is called yellow phosphorus. It is used in firework industry, in bombs, as Rodenticide. In South India, it is commonly available as rat killer paste (3%). The toxic dose of yellow phosphorous is 100 mg/kg body weight and toxicity increases when taken with a fatty meal. Yellow phosphorus causes hepatotoxicity by the production of phosphoric acid, which causes free radical damage. [2] This poisoning is associated with high mortality. The good prognostic factors are survival after 3 days and minimal elevation of LFT. Bad prognostic signs are altered sensorium, cyanosis, hypotension, metabolic acidosis, elevated prothrombin time, and hypoglycemia.

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The first phase consists of nausea, vomiting, abdominal pain, and smoking stools. Then, in the second phase, the patient may feel symptomatically better and the third stage consists of systemic organ damage due to absorbed phosphorous. Hepatotoxicity usually is recognized on the 3rd day by liver function test (LFT).[3] A large number of early deaths (<24 h) are due to cardiotoxicity. Renal toxicity is due to acute tubular necrosis which may be due to hypotension. Hyponatremia, hyperkalemia, and hyperphosphatemia are observed. Furthermore, there is no antidote for this poisoning. N-acetylcysteine is used as an antidote in paracetamol poisoning. Since its mechanism of hepatoprotective is similar, it can also be used in yellow phosphorous poisoning. N-acetylcysteine has been used in many of non-paracetamol-induced acute liver failure. N-acetylcysteine through replenishment of glutathione stores of superoxide dismutase (SOD) is proposed to have a beneficial effect. It replenishes the free radical scavenging system of hepatocytes and also directly neutralizes the free radicals. It is also said to improve cerebral perfusion in fulminant hepatic failure in rats. Many randomized control studies were not available for this poisoning.[4,5] Hence, this study was conducted to evaluate the efficacy of early N-acetyl cysteine from preventing the mortality.

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Aim

This study aims to evaluate the effectiveness of early N-acetylcysteine in reducing the mortality in rat killer paste poisoning.

METHODS

This study was conducted among 30 patients admitted with ingestion of rat killer paste poison in the Department of Medicine, Pudukkottai Government Medical College Hospital, from July 2018 to December 2018. This study is a prospective analytical study. Patients who ingested rat killer paste poison and age >12 years were included in the study. Patients are having jaundice, liver disease, congestive cardiac failure, patients on hepatotoxic drugs, and age <12 years were excluded from the study. Demographic details, medical history, and clinical examination were recorded. Complete blood count, blood sugar, renal function test, LFT, prothrombin time/international normalized ratio, and electrocardiography (ECG), and ultrasound abdomen were done. Patients were treated with N-acetylcysteine at the dosage of 150 mg/kg in 200 ml 5% D over 15 min and 50 mg/kg in 500 ml 5% D over 4 h and 100 mg/kg in 2000 ml 5% D over 16 h. There is no specific dosage of N-acetylcysteine for rat killer paste poisoning patients. Since N-acetylcysteine is used for many non-paracetamol causes of liver failure, we used N-acetylcysteine and there is no harm to patients. LFT was done daily until discharge to monitor the development of liver failure. Patients were categorized into three groups based on the time interval between consumption of poison and starting of N-acetylcysteine. There was no delay in starting of the N-acetylcysteine after admission.

RESULTS

In our study, among 30 patients studied, 17 were male and 13 were female. In that 19 patients were <30 years of age and nine patients were >30 years but <60 years. Two patients were >60 years [Figure 1].

Among 30 patients studied, five patients died, seven patients developed hepatitis, one patient developed acute kidney injury with hepatitis, and one patient developed hyponatremia. Of the patients developed complication, NAC was started within 6 h for 23 patients, 9 patients had complications, of which two died and NAC was started in >6–10 h for four patients, three had complications, of which two died and NAC was started in >10 h for three patients, one had complications and died.

In our study, of the 30 patients studied, 13 patients (43.34%) developed complication and in that 5 patients (16.67%) died. When comparing the time interval between starting of antidote and consumption of poison, 39.13% of patients developed complications and 22.23% of that patients died in <6 h group, but in 6–10 h group, 75% developed complications and mortality was 66.67%, whereas in >10 h group, 1 patient (33.33%) developed complication and died (100%) [Tables 1 and 2]

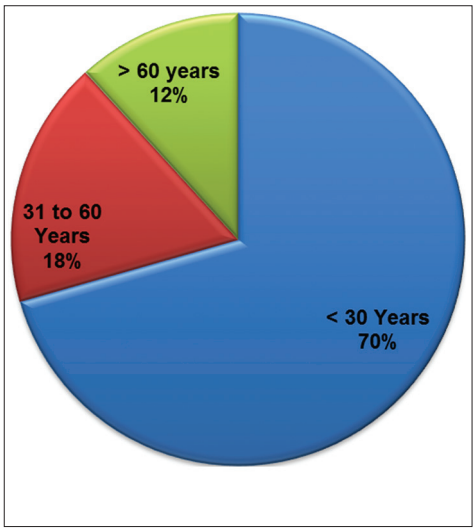

Figure 1: Age distribution

DISCUSSION

Various studies on poisoning did in India Banerjee *et al.* in West Bengal also noticed most commonly affected age group was 20–40 years.[6] Saoji *et al.* found in her study that the patients were usually asymptomatic during the initial 72 h of ingestion, or they may have signs and symptoms of gastrointestinal irritation.[7] Nalabothu *et al.* showed 35.7% mortality rate, whereas our study showed 17% mortality rate.[8]

Yellow phosphorus is a protoplasmic poison and is both hepatotoxic and cardiotoxic. The first phase consists of nausea, vomiting, abdominal pain, and smoking stools. Then, in the second phase, the patient may feel symptomatically better and the third stage consists of systemic organ damage due to absorbed phosphorous. Hepatotoxicity usually is recognized on the 3rd day by LFT. Ingestion of the large doses of yellow phosphorous can cause cardiotoxicity. A large number of early deaths (<24 h) are due to cardiotoxicity. ECG changes include corrected QT INTERVAL prolongation and ST segment changes which are associated with worse prognosis. Renal toxicity is due to acute tubular necrosis which may be due to hypotension.[8,9] Hyponatremia, hyperkalemia, and hyperphosphatemia are observed. The good prognostic factors are survival after 3 days and minimal elevation

Table 1: Correlation of time interval between the consumption of poison and starting of N-acetylcysteine with the development of complications

Time of starting N-acetylcysteine	Number of patients	Number of patients developed complications	Number of patients died after complications
<1 h	2	0	0
1–2 h	4	2	0
2–3 h	3	1	0
3–4 h	8	4	1
4–5 h	2	0	0
5–6 h	4	2	1
6–10 h	4	3	2
<10 h	3	1	1

Table 2: Comparison of three time interval groups and the development of complications and mortality

Time of starting N-acetylcysteine	Number of patients	% of patients developed complications	Number of patients died after complications (%)
<6 h	23	39.13%	22.23
>6–10 h	4	75	66.67
>10 h	3	33.33	100

of LFT.[10] Bad prognostic signs are altered sensorium, cyanosis, hypotension, metabolic acidosis, elevated prothrombin time, and hypoglycemia. N-acetylcysteine is used as a mucolytic, nephroprotective agent to prevent contrast-induced nephropathy, chronic obstructive pulmonary disease, and as an antidote in paracetamol poisoning. Since its mechanism of hepatoprotective is similar, it can also be used in yellow phosphorous poisoning. It acts as a glutathione substitute and replenishes the free radical scavenging system of hepatocytes and also directly neutralizes the free radicals.

CONCLUSION

As per our study after early N-acetylcysteine therapy, overall mortality has been reduced. However, there were no significant results in preventing the development of complications in patients started NAC within 6 h. To conclude from our study that there is strong evidence that early NAC therapy in rat killer paste poisoning has a significant impact in reducing the mortality.

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Original Article

Clinico-pathological Study of Pancytopenia: A Prospective Study

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Abstract

Background and Objectives: Pancytopenia is an important hematological entity. It is a disorder in which all three major formed elements of blood are decreased in number. The present study has been undertaken to find out various causes of pancytopenia by evaluation of bone marrow findings so that the data will help the clinician in better management of patients.

Materials and Methods: It was a prospective study conducted in the Department of Pathology in King George Hospital, Visakhapatnam, a teaching institute and tertiary hospital in over a period of 1 year. Patients were referred to pathology from the departments of medicine and pediatrics for investigations on suspicion of pancytopenia. The patients were evaluated clinically along with hematological parameters and bone marrow aspiration biopsy. It was carried out in 68 patients from November 2016 to December 2017. Hemogram was obtained using five-part automated analyzer. Bone marrow aspiration was performed using Salah needle from the posterior superior iliac crest and from the medial aspect of tibial tuberosity in children <4 years. Bone marrow aspiration smears were stained using Leishman's stain and Giemsa stain.

Results: Among the 68 patients studied, the age of the patients varied from 3 years to 76 years with a male predominance. Most of the patients presented with fever and generalized weakness. The most common physical finding was pallor. Dimorphic anemia was the predominant blood picture. The most common bone marrow finding was erythroid hyperplasia with megaloblastic maturation. The most common cause of pancytopenia was megaloblastic anemia (64.7% of cases) followed by hypersplenism (10.2% of cases). Other causes include aplastic anemia, leukemia, idiopathic thrombocytopenic purpura, tuberculosis, lymphoma, and multiple myeloma.

Conclusion: Detailed clinical history and physical examination along with hematological investigations and bone marrow aspiration biopsy are helpful for understanding the disease process and to diagnose the cause of pancytopenia. Identification of correct cause will help in implementing appropriate therapy. This study helps in identifying the incidence of various causes of pancytopenia.

Key words: Megaloblastic anemia, pancytopenia, bone marrow

INTRODUCTION

Pancytopenia is a disorder in which all three major formed elements if blood (red blood cell, white blood cell, and platelets) are decreased in number.[1] There are various trends in its clinical patterns, treatment modalities, and outcome.[2] It may be the manifestation of numerous disorders which primarily or secondarily affect the bone marrow.[3] The severity of pancytopenia and the underlying pathology determine the management and prognosis.[4] Thus, identifying the correct cause will help in implementing appropriate therapy.

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MATERIALS AND METHODS

The present study was conducted in the Department of Pathology in King George Hospital, Visakhapatnam, a teaching institute and tertiary hospital in over a period of 1 year from November 2016 to December 2017. It was a prospective study during which 68 cases were studied based on clinical evidence and hematological parameters. Patients were referred to pathology from the departments of medicine and pediatrics for investigations. Patients of all age groups and both genders were included. All of them underwent bone marrow aspiration biopsy.

Inclusion criteria were the presence of all three of the following:

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- Hb level <10 g/dL.
- TLC $<3.5 \times 10^9$/L.
- Platelet count $<100 \times 10^9$/L.

Exclusion criteria were the presence of the following:
- Patients who received blood and blood products.
- Patients on radiotherapy and chemotherapy.

Hematological parameters were obtained using five-part automated analyzer. Peripheral blood smears (PBS) were stained using methylene blue and examined under a microscope. Bone marrow aspiration biopsy was done by taking informed consent in a conventional manner. Bone marrow aspiration was performed using Salah needle from the posterior superior iliac crest and from the medial aspect of tibial tuberosity in children <4 years. Bone marrow aspiration smears were stained using Leishman's stain and Giemsa stain.

RESULTS

Among the 68 patients studied, 41 were male and 27 were female. A male preponderance was observed with a male to female ratio of 1.5:1. The age of the patients varied between 3 years and 76 years. There were a total of 12 pediatric cases among which 7 were males and 5 were females.

The following Table 1 demonstrates the age distribution of the patients in the study.

Patients presented with a wide variety of symptoms among which fever was most frequently observed.

Generalized weakness/fatigue was the second most common symptom. Pallor was seen in all the patients.

Presenting complaints and physical findings are presented in Table 2.

The causes of pancytopenia were ascertained after evaluating complete blood cell, PBS, and bone marrow aspiration findings.

Table 1: Age distribution of patients

Age group	Cases	Total (%)
≤10	6	8.9
11–20	17	25.3
21–30	9	13.4
31–40	12	17.9
41–50	10	14.9
51–60	8	10.4
61–70	5	7.4
71–80	1	1.4

The diseases diagnosed are mentioned in Table 3.

The following Graph 1 demonstrates the case distribution between males and females for each cause of pancytopenia.

Dimorphic anemia was the most common finding on PBS as was seen in 58.4% of the patients. Macrocytic anemia was observed in 13.8% of the patients with normocytic anemia and microcytic anemia observed in 13.3% and 12.3% of the cases, respectively.

Hematological parameters noted are mentioned in Table 4.

Megaloblastic anemia was the most common etiology of pancytopenia in this study. It was seen in 44 (64.7%) patients with a male to female ratio of 1.7:1. The age of the patients ranged from 15 to 65 years. Fever, generalized weakness, and fatigue were the common symptoms. Shortness of breath was seen in few cases. Bleeding p/v, malena, loss of weight, diarrhea, and vomiting were the other presenting complaints. Bone marrow aspiration showed erythroid hyperplasia with megaloblastic maturation in 86% of the cases. 14% of the cases showed dimorphic erythroid hyperplasia predominantly megaloblasts, and normoblasts. Vitamin B12 deficiency was proved to be the cause in 56.8% of the cases with low B12 levels. In 5% of the patients, alcoholism was the cause. No cause was established in the remaining cases.

Hypersplenism was the second most common cause of pancytopenia in this study. It was seen in 7 patients (10.2%) with a male to female ratio of 1.3:1. Patients were in the age group of 8 years to 45 years. The causes of hypersplenism were thalassemia (3 patients), sickle cell anemia (2 patients), and malaria (2 patients). Erythroid hyperplasia with both micronormoblastic and megaloblastic maturation was seen on bone marrow aspiration biopsy. Ring forms of Plasmodium were also seen in the bone marrow of a patient with malaria.

Aplastic anemia was diagnosed in 6 (8.8%) patients. Male to female ratio was 2:1. The age of the patients varied between 7 and 40 years. Bone marrow was hypocellular with an increase in adipose tissue. The causes were viral hepatitis, tuberculosis (TB), and idiopathic aplastic anemia. Viral hepatitis was observed in two patients. Extrapulmonary TB was seen in one patient. The patient presented with TB ascites, hepatosplenomegaly, mild pleural effusion, and retroperitoneal lymphadenopathy. In the remaining four cases, no cause was established hence diagnosed as idiopathic aplastic anemia. Fever, diarrhea, vomiting, and generalized weakness were the clinical complaints in idiopathic cases. Splenomegaly, fatigue, and shortness of breath were seen in another patient with idiopathic aplastic anemia.

Table 2: Presenting complaints and physical findings

Presenting complaints and physical findings	Percentage of cases (%)	Presenting complaints and physical findings	Percentage of cases (%)
Fever	40.2	Vomiting	11.9
Generalized weakness/fatigue	29.2	Lymphadenopathy	4.4
Abdominal pain	8.9	Loss of appetite	4.4
Pallor	100	Burning micturition	1.4
Splenomegaly	11.9	Ascites	1.4
Hepatomegaly	7.4	Weight loss	4.4
Jaundice	8.9	Gum bleeds	1.4
Body pains	5.9	Purpura	2.9
Pedal edema	10.4	Cough	5.9
Bleeding p/v	2.9	Chills and rigor	7.4
Diarrhea	2.9	Ulcer foot	1.4
Generalized edema	4.4	Malena	1.4

Table 3: Causes of pancytopenia

Causes of pancytopenia	Cases (% of total)
Megaloblastic anemia	64.7
Hypersplenism	10.2
Hemoglobinopathies	
Malaria	
Aplastic anemia	8.8
Idiopathic aplastic anemia	
Viral hepatitis	
Tuberculosis	
Leukemia	8.8
AML	
ALL	
CML	
Idiopathic thrombocytopenic purpura	4.4
Lymphoma	1.4
Multiple myeloma	1.4

CML: Chronic myelogenous leukemia, ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia

Leukemia was seen in 6 (8.8%) patients, among which 3 patients in the age range of 14–65 years were diagnosed with acute myeloid leukemia (AML), 2 male children aged 3 and 4 years with acute lymphoblastic leukemia (ALL), and one female patient aged 28 years with chronic myelogenous leukemia (CML). Male to female ratio was 2:1. Fever, shortness of breath, jaundice, loss of weight, HSM, purpura, and bleeding gums were the clinical findings in AML. The children with ALL had abdominal distension, generalized edema, and fever. On bone marrow aspiration, marked an increase in myeloid series with myeloblasts forming 70% of the differential count, male:female ratio of 20:1, with erythropoiesis suppression was observed in AML. In ALL, the bone marrow was infiltrated with lymphoid series predominantly lymphoblasts. CML showed a marked increase in myelopoiesis with the shift to left, myelocytes, and metamyelocytes forming 48% of the differential count and myeloblasts forming 4%. Male:female ratio was 20:1 with normoblastic erythropoiesis suppression.

The present study revealed idiopathic thrombocytopenic purpura as a cause of pancytopenia in 3 cases. Fever with chills and rigors, bleeding, and splenomegaly were the clinical findings. Megakaryoblasts were increased with premature forms - mono/bi/multinucleated seen in the bone marrow.

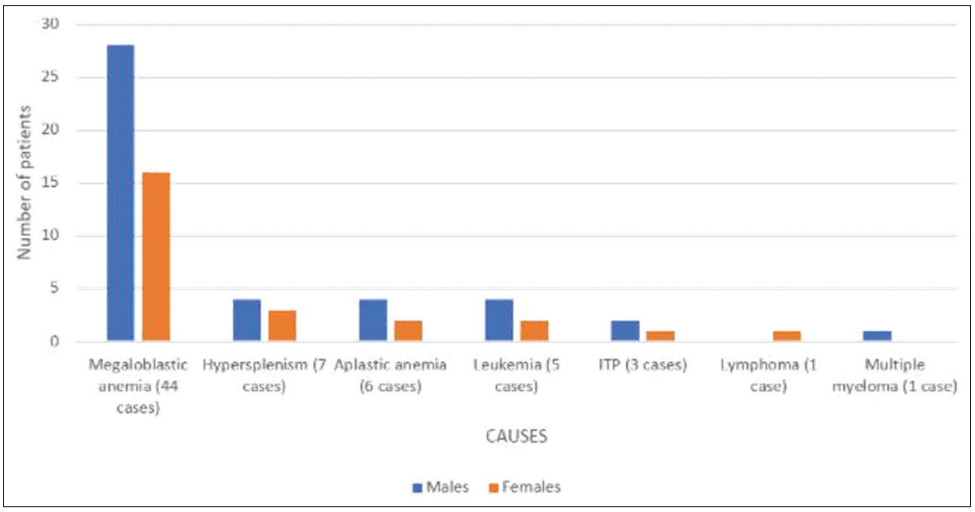
Lymphoma was encountered in a 16-year-old female. Atypical lymphocytes, myelocytes, and metamyelocytes were seen in the PBS. Bone marrow examination showed a marked increase in lymphopoiesis with immature cells of lymphoid series, showing large cells with cleaved, indented and folded nuclei, irregular clumping of chromatin, and few blast cells with uniformly distributed chromatin.

Multiple myeloma was the cause of pancytopenia in a 76-year-old male. The patient presented with an ulcer over left foot, fever, cough with expectoration, and shortness of breath and diffuses joint pains. Bone marrow showed both typical and atypical plasma cells, binucleated and multinucleated forms with intranuclear and cytoplasmic inclusions.

DISCUSSION

Decrease in hematopoietic cell production as a result of the destruction of bone marrow or replacement by abnormal tissue leads to pancytopenia.[5] In this study of 68 patients, the age of patients ranged from 3 years to 76 years with a male to female ratio of 1.5:1. The following Table 5 compares the gender ratio and the number of cases in various studies.

Fever was the most common presenting complaint and was observed in 40.2% of the patients followed by generalized weakness/fatigue which was seen in 29.2% of the patients. Similar findings were seen in a study by Khodke *et al.*,[15] where fever was seen in 40% followed by weakness (30%). In another study by Graham *et al.*,[22] fever was the most common symptom (37% of the cases) and generalized weakness was seen in 20% of the cases.



Graph 1: Sex distribution of patients

Table 4: Hematological parameters

Hematological	Megaloblastic	Hypersplenism	Aplastic	Leukemia	ITP
Parameters	Anemia		Anemia		
Hb (g/dL)	2.4–6.5	2.9–4.7	3.6–7.1	4.4–6.7	3.4–7
WBC (μL)	1200–3400	1100–3100	1400–3000	1400–2800	1300–3300
PC (μL)	21,000–98,000	14,000–90,000	10,000–94,000	40,000–98,000	10,000–40,000

WBC: White blood cell, ITP: Idiopathic thrombocytopenic purpura

Table 5: Age and gender comparison

Study	Number of cases	Age range	Male to female Ratio
Tilak and Jain, 1999	77	5–70	1.14:1
Khodke *et al*., 2000	50	3–69	1.3:1
Kumar *et al*., 2001	166	12–73	2.1:1
Khunger *et al*., 2002	200	2–70	1.2:1
Santra and Das, 2010	111	13–65	1.47:1
Subramanyam and Padma, 2015	106	4–75	1.12:1
Anjana *et al*., 2016	132	2.5–76	1.5:1
Present study	68	3–76	1.5:1

On PBS examination, dimorphic anemia (58.4%) was followed by macrocytic anemia (13.8%). In a study by Gayathri *et al*., predominant blood picture was dimorphic anemia (37.5%) followed by macrocytic anemia (31.7%). Hypersegmented neutrophils were seen in 42.4% of the patients in this study. Graham *et al*. reported a much higher percentage of hypersegmented neutrophils (51.35%) whereas Khunger *et al*. demonstrated an absence of hypersegmented neutrophils on PBS in his study.

The most common cause of pancytopenia in this study was megaloblastic anemia followed by hypersplenism. The following Table 6 compares the important causes of pancytopenia in various studies.

The most common cause of pancytopenia reported in the majority of studies from various parts of the world has been megaloblastic anemia.[6] It is a rapidly correctable disorder and should be promptly notified.[7] Megaloblastic anemia has the highest incidence in this study and was seen in 64.7% of the patients. Similarly, Tilak *et al*. reported an incidence of 68% and the study by Gayathri *et al*.[14] revealed an incidence of 74%.

In hypersplenism, there is peripheral pooling or trapping and destruction in an enlarged spleen resulting in cytopenias.[8] A second most common cause, in this study, was hypersplenism, and its incidence was 10.2%. Much alike, in the study by Sharma *et al*., the incidence of hypersplenism stood at 10.6%. The causes of hypersplenism were thalassemia (3 patients), sickle cell anemia (2 patients), and malaria (2 patients) in this study. Pereira *et al*.[18] reported one case each of paroxysmal nocturnal hemoglobinuria, malaria, and mastocytosis causing hypersplenism whose incidence was 6.25% in their study.

Malaria, especially *Plasmodium Falciparum,* may cause pancytopenia as a result of hypersplenism, immune hemolysis, disseminated intravascular coagulation, hemophagocytosis, impairment of marrow function or direct marrow invasion by the parasite.[9] 2.9% of the cases were due to malaria in this study compared to 1.93% in the study by Gayathri *et al*. and 1% in that of Khunger *et al*.

The incidence of aplastic anemia in this study was 8.8%. Tilak and Jain *et al*. revealed a comparable incidence of aplastic

Table 6: Comparison of important causes of pancytopenia

Study	Most common etiology (% of cases)	Second most common cause (% of cases)
Tilak and Jain, 1999	Megaloblastic anemia (68)	Aplastic anemia (7.7)
Khodke *et al*., 2000	Megaloblastic anemia (44)	Aplastic anemia (14)
Khunger *et al*., 2002	Megaloblastic anemia (72)	Aplastic anemia (29.51)
Kumar *et al*., 2001	Aplastic anemia (29.51)	Megaloblastic anemia (22.28)
Santra and Das, 2010[17]	Aplastic anemia (20)	Hypersplenism (11.7)
Subramanyam and Padma, 2015[23]	Megaloblastic anemia (26.42)	Hypersplenism (24.53)
Anjana *et al*., 2016[19]	Megaloblastic anemia (50.7)	Hypersplenism (10.6)
Present study	Megaloblastic anemia (64.7)	Hypersplenism (10.2)

anemia (7.7%) in their study. However, Khodke *et al.* disclosed a much larger incidence which stood at 14%. The causes of aplastic anemia in this study were viral hepatitis, disseminated TB, and idiopathic aplastic anemia. Viral hepatitis as a cause of aplastic anemia was observed in 2 patients in this study. Jain *et al.* described one case of viral hepatitis as a cause of pancytopenia. The incidence of idiopathic aplastic anemia was identified at 4.4% whereas Jain *et al.* reported an incidence of 3.2% for idiopathic aplastic anemia.

The pathogenesis of pancytopenia in TB has intrigued both physicians and pathologists for years, the exact pathology being not known.[10] TB constituted 2.9% of the cases in this study. Likewise, Khunger *et al.*[16] and Kumar *et al.* described only one case of TB in their studies each, making TB one of the rare causes of pancytopenia.

In leukemia, the pathophysiology is related to a combination of suppression of the normal hematopoiesis and replacement of bone marrow by leukemic cells resulting in pancytopenia and immunosuppression.[11] We encountered 3 cases of AML (4.4%), 2 cases of ALL (2.9%), and 1 case of CML (1.4%), totaling 8.8%. Only 3.4% of the cases had subleukemic leukemia in a study by Para *et al.*, however, Graham *et al.*, reported a much higher incidence of AML (13.3%) and 3.3% was that of ALL.

Present study divulged idiopathic thrombocytopenic purpura (ITP) as a cause of pancytopenia in 3 cases (4.4%). In a study by Rajesh Para *et al.*,[21] 1.7% of the patients had ITP, and its incidence was observed at 10.5% in the study by Pudasaini *et al.*[20]

One case of non-Hodgkin's lymphoma was encountered in this study (1.4%). Non-Hodgkin lymphoma (NHL) is known to infiltrate bone marrow more commonly than Hodgkin's and thus leading to pancytopenia.[12] Jain *et al.* found NHL to be a cause of pancytopenia in 0.8% of the cases in their study making it a less common cause of pancytopenia.

Patients with multiple myeloma develop pancytopenia due to the replacement of bone marrow by immunoproliferative cells.[13] Multiple myeloma was diagnosed in a single case (1.4% of the cases) in this study. In a similar way, Tilak and Jain *et al.* disclosed a single case of multiple myeloma as a cause of pancytopenia. 3.5% of the patients showed pancytopenia in the study by Pudasaini *et al.*

CONCLUSION

Pancytopenia is a very important hematological problem and should be kept in mind when diagnosing a patient with unexplained fever, generalized weakness, and fatigue. There are numerous causes most frequent of which is B12/folate deficiency which can achieve spontaneous remission on treatment. It should be remembered that idiopathic thrombocytopenic purpura can also present with pancytopenia. The prognosis can be bad if the diagnosis of pancytopenia is missed and untreated and hence all the causes of pancytopenia, even those uncommon, are equally important. Detailed clinical history and physical examination along with hematological investigations and bone marrow aspiration biopsy are needed to evaluate and assess the cause of pancytopenia. Identification of correct cause will help in implementing appropriate therapy. This study has helped us to identify the incidence of different causes of pancytopenia in a tertiary hospital in South India.

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Original Article

Intralesional Bleomycin for Lymphangioma: An Effective Alternative Non-surgical Therapy

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Abstract

Introduction: Conventionally, lymphangiomas have been managed by surgical excision which range from simple excision to extensive compartmental exenteration.With the advent of the usefulness of sclerotherapy, especially bleomycin, management of extensive lymphangiomas which are hitherto considered inoperable cases has become very comfortable for patient and surgeon.

Materials and Methods: A total of 28 patients were included in the study. Neck was the most common site of involvement followed by axilla; groin was involved in two cases. Injection bleomycin was reconstituted and diluted, a dose of 0.5 IU/Kg injected intralesionally after aspirating an equal volume of fluid. Compression bandage was applied for 24 h. Cases were reviewed after 3 weeks for assessing clinical and serological response.

Results: Significant reduction of mass was noted in 68% of cases (*n* = 19). Surgery was required in 7% (*n* = 2), complete regression of mass was noted in the remaining 25% (*n* = 7) cases.

Conclusion: This modality of treatment may be used safely as primary modality of treatment for select group of patients.

Key words: Bleomycin, Lymphangioma, Sclerotherapy

INTRODUCTION

Lymphangioma is a unilocular or multilocular congenital malformation of lymphatic system occurring in approximately 1 in 6000-12000 births. [1] It can lead to morbidity due to cosmesis, compression of adjacent organs infection, hemorrhage, rupture, and sinus formation.[1,6] Surgery is the mainstay of treatment but has unacceptable rates of complications and morbidity.

Certain newer modalities of treatment have been studied in the past few years, of which intralesional bleomycin therapy has been proved to be highly effective and safe mode of treatment. We present our series of 28 cases of the lymphangiomas treated at our institute which are primarily treated by intralesional bleomycin sclerotherapy.

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MATERIALS AND METHODS

A total of 28 cases of lymphangiomas were diagnosed and treated between 2015 and 2018 at our Institute Rangaraya Medical College, Kakinada. In all cases, diagnosis was established by clinical features sonological and cytological findings. Computed tomography/magnetic resonance imaging was needed in few cases to assess the extent of lesion, particularly into thorax or abdomen. Bleomycin injection[2,4,5,10] was used in all cases at a dose of 0.5 IU/Kg body weight after diluting with normal saline to make the required volume average numbers of injections needed were around three in most cases.

The injection was done in the operation theater under sedation after aspirating an equal quantity of lymphangioma fluid [Figure 1a-c]. Multiple site injections were made as most of them are multiloculated. Response was observed by serial photographs and imaging studies.

RESULTS

Of 28 cases, there was a significant response in 19 cases (68%), good response was noted in 7 cases (25%), and

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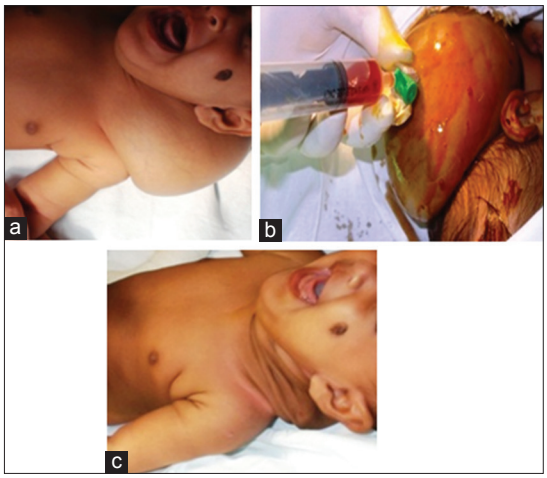

Figure 1: (a) Extensive lymphangioma, (b) method of injection, (c) immediate result

poor response two cases which required surgical excision.

DISCUSSION

Lymphangiomas are common developmental anomaly of the lymphatic system, the most common site is head and neck, of 28 cases, 18 cases were male and 10 cases were female.

Treatment of lymphangioma is highly challenging. Although surgical excision offers the opportunity for permanent cure by excising the lesion completely, it is practically difficult to achieve this goal by sparing the vital neurovascular structure in many cases.

Recurrences and not so cosmetic outcomes are quite common after surgical procedure in extensive lesions.

In the past two decades, many case series have been reported using sclerosants such as OK-432,[11,12] bleomycin, and other sclerosants with great success.[1]

Bleomycin is easily available economical and virtually no side effects were reported with intralesional use.

In our study, intralesional bleomycin resulted in significant reduction of size in 68% of case and complete resolution in 25% of cases.

Only side effects noted in our study were initial swelling and signs of local inflammation which settled down with oral paracetamol.

The most dreaded complication of bleomycin is pulmonary toxicity/retroperitoneal fibrosis. This complication has been noted only in subjects who received >400 IU. Hence, the fear of this complication does not arise in the treatment of lymphangioma as the dose used is very small.

CONCLUSION

Our series concludes that intralesional bleomycin is a very safe and effective method of treating lymphangiomas, thereby avoiding morbid consequences of surgical excision, especially in extensive lesions.

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Original Article

Efficacy of Teneligliptin as Add-on Therapy in Patients with Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Real-World Experience

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) with chronic kidney disease (CKD) is dreadful combination necessitating adequate glycemic control to prevent further complications. Teneligliptin is found to be renal friendly antidiabetic agent which can provide effective glycemic control.

Objective: The objective of this study was to determine the efficacy of teneligliptin as add-on to existing therapy in patients of T2DM with CKD.

Materials and Methods: This was a retrospective study where patients with T2DM and CKD who received teneligliptin were included in the study. Changes in glycemic parameters such as hemoglobin A1c (HbA1c) (%), fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) and change in estimated glomerular filtration rate (eGFR) were analyzed.

Results: In total, 66 patients were included in analysis. Mean age was 57.7 ± 14.0 years and 60.6% were males. Baseline HbA1c, FPG, and PPG levels were 7.8 ± 0.7%, 128.0 ± 25.5 mg/dl, and 214.0 ± 55.9 mg/dl, respectively. There was a significant reduction in HbA1c at 3 and 6 months (mean difference from baseline: −0.9 ± 0.5 and −1.2 ± 0.5 respectively, $P < 0.001$ for both). Similarly, mean change in FPG (−28.4 ± 20.9 and −29.9 ± 24.3 mg/dl, respectively) and PPG (−70.5 ± 49.2 and −97.0 ± 60.7 mg/dl, respectively) was also significant ($P < 0.001$ for all comparisons). The change in eGFR was significant at 3 months ($P = 0.049$) and 6 months ($P = 0.014$).

Conclusion: Teneligliptin is effective in reducing glycemic burden in patients with T2DM and CKD and can be considered as be considered among first choices for glycemic control in patients with renal impairment.

Key words: Estimated glomerular filtration rate, Hemoglobin A1c, Renal failure, Teneligliptin

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is rapidly growing epidemic in India. It is well known that the level of glycemia is associated with complications of T2DM. Nephropathy is a major microvascular complication of T2DM. A recent study from India reported nephropathy in 43% of newly diagnosed T2DM cases.[1] Decline in renal function in T2DM demands careful selection of renal-friendly agents. Among various gliptins, teneligliptin is being used widely in India setting since its approval in 2015.[2] Teneligliptin kinetics are not altered with any degree of renal dysfunction and therefore make it a suitable agent for T2DM management in chronic kidney disease (CKD) at all stages.[3] Glycemia lowering efficacy of teneligliptin as add-on treatment to monotherapy and dual or triple drug therapy is already proven.[4]

With teneligliptin use in CKD, there are relatively scarce clinical studies in Indian setting. A study from Mumbai, India, reported a significant glycemia lowering efficacy

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of teneligliptin in CKD patients at 12 and 24 weeks.[5] However, the study consisted of small sample. Therefore, more studies are necessary for assessing teneligliptin efficacy and safety in CKD patients with T2DM. We report here the experience of using teneligliptin in CKD patients in our hospital setting.

MATERIALS AND METHODS

Study Setting

This study was conducted at a diabetology clinic from Central India. This clinic provides all the services in the field of medicine and diabetology. Patients with T2DM are among the most frequently visiting patients in this clinic.

Study Design

This was a single-center, retrospective, observational study where data from patient records were analyzed.

Study Population

Adult (>18 years of age) patients of T2DM with CKD in all stages who were prescribed teneligliptin in addition to their existing therapy were included for analysis. CKD was already diagnosed in these cases based on estimated glomerular filtration rate (eGFR) and/or presence or absence of microalbuminuria. Patients were included in analysis irrespective of their hemodialysis status.

Study Objective

The objective of this study was to determine the efficacy of teneligliptin in patients of T2DM with CKD at 3 and 6 months after initiation of teneligliptin. The efficacy parameters analyzed were hemoglobin A1c (HbA1c, (%), fasting plasma glucose (FPG, mg/dl), and postprandial plasma glucose (PPG, mg/dl).

Data Collection

Data from patients' records over 1-year period between April 2017 and March 2018 were collected in a pre-defined structured pro forma. Data on demographic parameters such as age, sex, and presence of different comorbid conditions were noted. Details of T2DM such as duration, current treatment, levels of HbA1c, FPG, and PPG were also noted. Available values of eGFR were identified and recorded. The details were assessed at baseline (at the time of start of treatment), after 3 months, and after 6 months of teneligliptin treatment. All the investigations were performed at a single laboratory. In all the patients, eGFR estimation was done as per the CKD Epidemiology Collaboration (CKD-EPI) equation.

Statistical Analysis

The data were entered into Microsoft Excel sheet and were analyzed with the same. Categorical variables were presented as frequency and percentages. Continuous variables were presented as mean and standard deviation. Student *t*-test was applied to identify the change in HbA1c, FPG, PPG, and eGFR from baseline to 3 and 6 months. Percentage of patients achieving target HbA1c <7% was assessed at 3 and 6 months. $P < 0.05$ was considered to be statistically significant.

RESULTS

There were a total of 66 patients included in the analysis. Mean age of the patients was 57.7 ± 14.0 years and 60.6% were males. Hypertension (62.1%) was the most frequent comorbid condition observed in study patients. Mean duration of T2DM was 11.0 ± 7.8 years. Among antidiabetic drugs, sulfonylureas (glimepiride - 60.6% and gliclazide - 16.2%) and metformin (48.5%) were commonly prescribed. The baseline characteristics are shown in Table 1.

Table 2 describes the changes in glycemic parameters. At baseline, mean HbA1c level was 7.8 ± 0.7%. There was a significant reduction in HbA1c at 3 months (6.9 ± 0.5%, mean difference: −0.9 ± 0.5%, $P < 0.001$) and further reduction was seen at 6 months (6.6 ± 0.4%, mean difference: −1.2 ± 0.5%, $P < 0.001$). As there was loss of data at 6 months, we analyzed the FPG and PPG change considering the baseline of evaluable patients. At 3 months, FPG reduced from 128.0 ± 25.5 mg/dl at baseline to 99.6 ± 9.2 mg/dl at 3 months (mean difference:

Table 1: Baseline characteristics

Characteristics	Observation (*n*=66)
Age (years)	
Mean±SD	57.7±14.0
Age groups	
≤50	24 (36.4)
51–60	15 (22.7)
61–70	16 (24.2)
>70	11 (16.7)
Gender	
Males	40 (60.6)
Females	26 (39.4)
Comorbidities	
Hypertension	41 (62.1)
Dyslipidemia	8 (12.1)
Ischemic heart disease	4 (6.1)
Cerebrovascular disease	3 (4.5)
Duration of diabetes (years)	11.0±7.8
Antidiabetic medications	
Metformin	32 (48.5)
Glimepiride	40 (60.6)
Gliclazide	11 (16.2)
Alpha-glucosidase inhibitors	19 (28.7)
Insulin	8 (12.1)
Pioglitazone	4 (6.1)
Hemodialysis	2 (3.0)

Data presented as frequency (%) and mean±SD

Table 2: Change in glycemic parameters

Parameter	Baseline (*n*=66)	3 months (*n*=66)	Baseline (*n*=27)	6 months (*n*=27)
HbA1c (%)				
Mean±SD	7.8±0.7	6.9±0.5	7.8±0.7	6.6±0.4
Change from baseline		−0.9±0.5*		−1.2±0.5*
FPG (mg/dL)				
Mean±SD	128.0±25.5	99.6±9.2	126.5±24.2	96.6±5.0
Change from baseline		−28.4±20*		−29.9±24.3*
PPG (mg/dL)				
Mean±SD	214.0±55.9	143.5±24.5	236.8±57.6	139.8±13.8
Change from baseline		−70.5±49.2*		−97.0±60.7*

FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, SD: Standard deviation. *P<0.001

Table 3: Change in eGFR

eGFR	Values		
	Baseline	3 months (*n*=57)	6 months (*n*=22)
Baseline of patients assessed at 3 months	80.4±25.3	81.1±24.7	-
Baseline of patients assessed at 6 months	77.3±25.6	-	79.3±24.8
Change from baseline		0.70 (P=0.049)	2.0 (P<0.014)

Data presented as mean±SD

−28.4 ± 20.9 mg/dl, $P < 0.001$) and from 126.5 ± 24.2 mg/dl to 96.6 ± 5.0 mg/dl at 6 months (mean difference: −29.9 ± 24.3 mg/dl, $P < 0.001$). Reduction in PPG was also significant at 3 months (mean difference: −70.5 ± 49.2 mg/dl, $P < 0.001$) and 6 months (mean difference: −97.0 ± 60.7 mg/dl, $P < 0.001$) follow-up. At baseline, only 7.6% of patients had HbA1c <7%. After addition of teneligliptin, proportion of patients achieving HbA1c <7% increased to 57.6% at 3 months and further to 73.1% at 6 months [Figure 1].

Table 3 describes the changes in eGFR levels. There was mild but significant increment in eGFR at 3 months (mean change: 0.70 ml/min/1.73m^2, $P = 0.049$) as well as at 6 months (mean change: 2.0 ml/min/1.73m^2, $P < 0.014$).

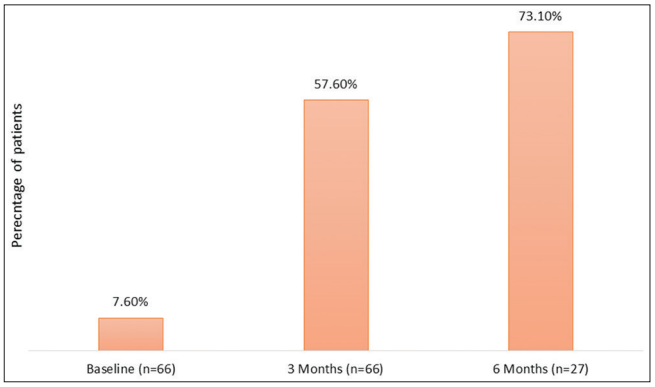

Figure 1: Proportion of patients with target hemoglobin A1c (<7%)

DISCUSSION

T2DM is a major etiological factor for kidney disease. Most of the antidiabetic agents have restrictions for their use if eGFR falls to <30 ml/min/1.73m^2. Teneligliptin, on the other hand, does not require dose adjustment even in end-stage renal disease.[3] Addition of teneligliptin in our study was found to provide a significant reduction in HbA1c, FPG, and PPG. Mean reduction of HbA1c was −0.9% at 3 months and −1.2% at 6 months after addition of teneligliptin. A study from Shah in CKD patients with T2DM (n = 37) reported HbA1c reduction of 0.48% (P = 0.001) and 1.0% (P = 0.001) at 3 and 6 months, respectively.[5] Reduction in FPG and PPG also significant confirming teneligliptin efficacy in all three glycemic parameters. Another evaluation from Otsuki *et al.* reported that teneligliptin is efficacious in lowering glucose levels significantly even in patients on hemodialysis (HD) and it was seen in patients started newly on teneligliptin or switched from voglibose or vildagliptin. Reduction in HbA1c was 0.3–0.8% at 24 weeks after initiating teneligliptin.[6] Wada *et al.* also reported similar finding with significant glycemia lowering efficacy of teneligliptin in patients on HD.[7] A large, post-marketing surveillance study from Japan also confirmed the efficacy of teneligliptin in providing significant HbA1c reduction at 1 year (−0.68 –−0.85% across different eGFR groups after adjusting for baseline HbA1c) and 2 years (−0.71–−0.85% across different eGFR groups after adjusting for baseline HbA1c).[8] Teneligliptin was used as an add-on to therapy with various antidiabetic agents as shown in Table 1. This suggests that the addition of teneligliptin is helpful in lowering glycemic burden in CKD patients. Teneligliptin has shown to lower insulin dosage and reduce hypoglycemic events in patients on HD treated with insulin.[9] These evidence strongly point out that teneligliptin should be

considered from the early phase of renal insufficiency in patients with T2DM.

When considering target HbA1c in patients of T2DM with renal impairment, individualized target levels are advised considering overall health of the patient.[10] An observational study in patients of CKD without dialysis showed U-shaped relationship of HbA1c with mortality. HbA1c of >9.0% and <6.5% showed increased mortality.[11] This suggests that individualized target should be considered. We observed that, after the addition of teneligliptin, HbA1c target of <7% was achieved among 57.6% and 73.1% of patients assessed at 3 and 6 months, respectively. Although the target HbA1c values are unclear in patients of CKD with or without dialysis, a general target of <7% might be helpful in reducing other potential microvascular and macrovascular complications of T2DM.[10]

The renal function as assessed by eGFR showed significant improvement at 3 and 6 months. Although teneligliptin has no effect on eGFR, the positive change observed is probably secondary to the improvement in glycemic burden. Shah also reported a significant improvement in eGFR from 53.35 ± 4.24 ml/min/1.73m^2 to 55.08 ± 4.19 and 57.95 ± 4.36 ml/min/1.73m^2 at 3 and 6 months, respectively ($P = 0.001$ for both comparisons).[5] However, evidence from post-marketing surveillance study from Haneda *et al.* reported relatively stable eGFR levels over 1 and 2 years with no significant change after initiating teneligliptin.[8] Another evaluation reported no significant difference in eGFR change when compared to sitagliptin at 24 weeks. However, teneligliptin and not sitagliptin improved endothelial function and reduced renal and vascular oxidative stress.[12] These findings suggest that teneligliptin can be among the first choices for glycemic control in T2DM with renal impairment.

Limitations

The study was limited by retrospective design, small sample size, and missing data on follow-up. Assessment of microalbuminuria may have provided more insights into the understanding of preservation or reversal of renal impairment. Detailed analysis of glycemia lowering efficacy according to different eGFR levels was not possible due to the loss of data on follow-up visits. A comparative analysis among different drug combinations and with other gliptins can further provide a better understanding of drug combinations for achieving optimal glycemic lowering in renal impairment.

CONCLUSION

Our retrospective analysis in patients of T2DM with CKD suggests that teneligliptin effectively provides a reduction in HbA1c as well as fasting and post-prandial glucose. The renal function during teneligliptin treatment improved over 6-month period possible due to improvement in glycemic burden. Teneligliptin can, thus, be considered among the first-choice treatments for T2DM with any degree of renal impairment.

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Original Article

Effect of Teneligliptin on QT Interval in Type II Diabetes Mellitus Patients: A Retrospective Evaluation

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Abstract

Background and Aim: According to a strict QT/QTc evaluation study and clinical studies for type 2 diabetes conducted in Japan and other countries, NO AEs related to QT prolongation were detected with 40 mg/day of teneligliptin, which is the maximal dosage used in clinical practice. So far, there are no data regarding the safety of teneligliptin in Indian type 2 diabetic patients with respect to QTc prolongation. Therefore, the study was conducted to evaluate the safety of teneligliptin in type 2 diabetic patients with respect to QT prolongation.

Methods: A retrospective data were collected from type 2 diabetes mellitus patients with electrocardiogram (ECG) records who were treated with teneligliptin along with ongoing treatment. Primary endpoint was to compare the change in the ECG at 3 months from the baseline from the collected data. Mean daily dose (MDD) of antidiabetic drugs, HbA1c, fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) was also analyzed.

Results: A total of 49 patients' data were collected and analyzed with a mean age of 55.5 years and mean duration of diabetes 9.3 years. Hypertension was the most common comorbid disease (63.3%) along with diabetes for a mean duration of 10.0 years. Metformin plus glimepiride were the most prescribed dual drugs (63.3%) along with teneligliptin with an overall MDD of metformin (1065.2 mg) and glimepiride (2.1 mg). From the collected data, there was significant reduction in FPG and PPG at 3 months which were 49.6 mg/dL *(*$P < 0.0001$) and 100.5 mg/dL *(*$P < 0.0001$) reduction observed from the baseline, respectively. Significant changes were observed in the HbA1c from the baseline to 3 months (0.9%, $P < 0.0001$). There was no significant increase in the mean QTc interval from baseline to 3 months. No serious adverse events or hypoglycemia were reported.

Conclusion: Teneligliptin was well tolerated with no significant change in QTc prolongation and significantly effective in reducing the FPG, PPG, and HbA1c at 3 months from the baseline with no adverse events. There was no increase in the mean QT interval.

Key words: Diabetes, Teneligliptin, QT interval

INTRODUCTION

Diabetes mellitus, characterized by abnormally high blood sugar (glucose) level, is one of the leading global health issues of the 21st century.[1] Type 2 diabetes mellitus (T2DM) constitutes more than 95% of all the diabetic populations.[2] T2DM is a well-known risk factor for cardiovascular (CV) disease, with almost 50% of patients developing heart failure, and those with both diabetes and established heart failure have more severe outcomes.[3] Hence, selecting the optimal therapy for individuals with T2DM requires cautious consideration regarding CV safety of glucose lowering therapies.

There have been persistent concerns about potential adverse CV effects of oral hypoglycemic agents. In 2008, the US Food and Drug Administration responded to this need by issuing guidelines that mandate a thorough assessment of CV risk in glucose lowering drugs.[4] Apart from glucose-lowering effect, dipeptidyl peptidase-4 (DPP4) inhibitors have a diverse impact on CV system. This impact is due

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to the presence of glucagon-like peptide-1 receptors in human cardiac myocytes which is well documented for the past two decades.[5]

Teneligliptin, a DPP4 inhibitor, was approved for the management of T2DM in Japan (2012), South Korea (2014), and India (2015).[1] In addition to effective glycemic control, the results of various clinical trials also suggested that teneligliptin, as monotherapy or add-on therapy, was generally well tolerated in patients with T2DM.[1] It was associated with improvements in left ventricular function - particularly diastolic - and endothelial functions, as well as with an increase in serum adiponectin levels.[6] No CV side effects were ever reported with the molecule at a normal therapeutic dose, but mild QTc transient prolongation was documented while using teneligliptin in supraclinical dosages of 160 mg per day.[7] Significant QTc prolongation has not been reported with teneligliptin 20 as well as 40 mg in various Japanese studies. However, there are no studies for QTc prolongation in Indian diabetic patients.

Therefore, the present retrospective analysis was undertaken to evaluate the effect of teneligliptin on QT interval in T2DM patients in real-world setting.

METHODS

This was a retrospective, single-centric study conducted in T2DM patients who were prescribed teneligliptin 20 mg once daily as a monotherapy or add-on therapy with other OADs for at least 3 months. Patients with available data for fasting plasma glucose (FPG), postprandial plasma glucose (PPG), HbA1C, and electrocardiogram (ECG) at baseline, 1st month, and 3rd month were enrolled in the study. QT interval in the ECG is a measure of cardiac repolarization and any drug that increases the QT interval may increase the risk of CV events, and hence, QT interval was focused in ECG in the present study. Confidentiality of the data was maintained throughout the study period. The data were captured and compiled in Microsoft Excel version 2013. Categorical data were expressed in percentage and mean ± SD; paired *t*-test was used to look for the statistical difference at baseline and $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 49 patients were enrolled for data analysis, to evaluate the effect of teneligliptin on QT interval. The average age of patients was 55.5 years with the mean duration of diabetes being 9.3 years. Hypertension was the most common comorbidity in 63.3% of patients followed by dyslipidemia (32.7%) and stroke (10.2%) [Table 1]. Metformin and glimepiride were the two most common drugs prescribed along with teneligliptin. The average daily dose of metformin and glimepiride prescribed was 1065.2 mg and 2.1 mg, respectively [Table 2]. Metformin and glimepiride was the most common fixed-dose combination prescribed along with teneligliptin in 63.3% of patients [Table 3].

Among the enrolled patients, baseline mean FPG level was 147.9 ± 38.4 mg/dl, which decreased to 115.7 ± 19 mg/dl at the end of 1st month and 98.3 ± 5.8 mg/dl at the end of 3rd month. A significant difference was seen in the mean FPG at baseline and at the end of 1st month ($P \leq 0.0001$) and 3rd month ($P \leq 0.0001$). The mean PPG level was 256.2 ± 63.3 mg/dl at baseline which decreased to 184 ± 18.3 mg/dl and 155.7 ± 13.9 mg/dl at the end of 1st month and 3rd month, respectively. A significant difference was seen in the mean PPG at baseline and 1st month ($P \leq 0.0001$) and 3rd month ($P \leq 0.0001$). Mean HbA1C level was 7.6 % ± 0.9 % at baseline and decreased significantly ($P \leq 0.0001$) to 6.7% ± 0.9% at the end of 3rd month. Mean QT interval was 407.1 ± 27.8 ms at baseline and 407.1 ± 29.3 ms and 407.8 ± 27.6 ms at the end of 1st month and 3rd month, respectively. No significant difference was seen in the mean QTc at

Table 1: Comorbidities among enrolled patients

Comorbidities	Mean (years)	Number of patients (%)
Hypertension	10.0	31 (63.3)
Dyslipidemia	8.3	16 (32.7)
Stroke	7.6	5 (10.2)
CAD/ACS/IHD*	5	2 (4.1)

*CAD: Coronary artery disease; ACS: Acute coronary syndrome; IHD: Ischemic heart disease

Table 2: Concurrent medication prescribed among enrolled patients

Concurrent medication	Mean dose	Number of patients (%)
Metformin	1065.2	46 (93.9)
Glimepiride	2.1	35 (71.4)
Gliclazide	67.5	4 (8.2)
Pioglitazone	12.9	7 (14.3)
Dapagliflozin	5	4 (8.2)
Miglitol	10	1 (2.0)
Voglibose	0.6	3 (15.0)

Table 3: Combinations prescribed among study participants

Combination	Number of patients (%)
Metformin+Glimepiride	31 (63.3)
Metformin+Glimepiride+Dapagliflozin	2 (4.1)
Metformin+Glimepiride+Dapagliflozin+Voglibose	1 (2.0)
Metformin+Glimepiride+Voglibose	1 (2.0)

Table 4: FPG, PPG, HbA1C, and ECG at baseline, 1st month, and 3rd month

Parameters	FPG	PPG	HbA1C	QTc
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Baseline visit	147.9±38.4	256.2±63.3	7.6±0.9	407.1±27.8
Follow-up visit at 1 month	115.7±19	184±18.3	NA	407.1±29.3
Changes from baseline	32.2±19.4*	72.2±45*	NA	0±1.5#
Follow-up visit at 3 months	98.3±5.8	155.7±13.9	6.7±0.5	407.8±27.6
Changes from baseline	49.6±32.6*	100.5±49.4*	0.9±0.4*	0.7±0.2@

*P<0.0001; #P=0.99; @P=0.69. SD: Standard deviation, FPG: Fasting plasma glucose, PPG: Postprandial plasma glucose, ECG: Electrocardiogram

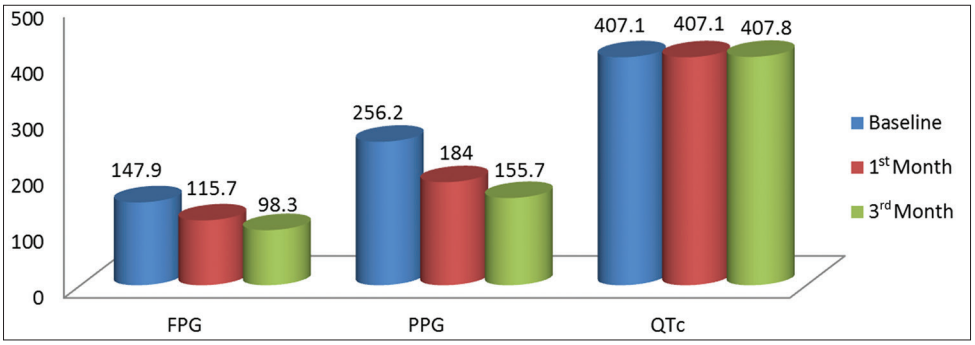

Figure 1: Fasting plasma glucose, postprandial plasma glucose, and electrocardiogram at baseline, 1st month, and 3rd month

baseline and 1st month (P = 0.99) and 3rd month (P = 0.69) [Table 4 and Figures 1 and 2]. There were no clinically relevant drug–drug interactions reported when teneligliptin was coadministered with other antidiabetic drugs.

DISCUSSION

An undesirable property of some non-antiarrhythmic drugs is their ability to delay cardiac repolarization, an effect that can be measured as prolongation of the QT interval on the surface ECG. There is a qualitative relationship between QT prolongation and the risk of TdP (polymorphic ventricular tachyarrhythmia), especially for drugs that cause substantial prolongation of the QT interval. The "thorough QT/QTc study" is thus intended to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation.[8] The threshold level of regulatory concern is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms.[8] Drugs that prolong the mean QT/QTc interval by around 5 ms or less do not appear to cause TdP, while drugs that prolong the mean QT/QTc interval by >20 ms have a substantially increased likelihood of being proarrhythmic. The data on drugs that prolong the mean QT/QTc interval by more than around 5 and <20 ms are inconclusive, but some of these compounds have been associated with proarrhythmic risk.[8]

In the present QTc study, data from 49 T2DM patients on teneligliptin monotherapy or combination therapy

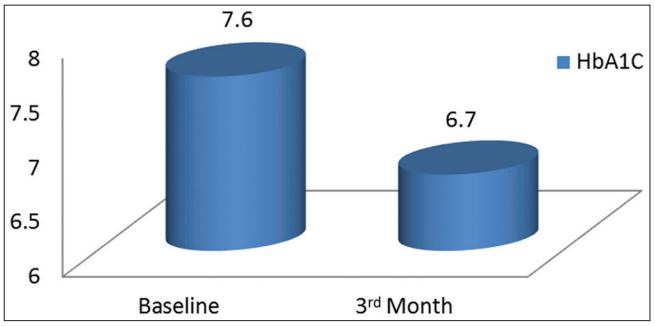

Figure 2: HbA1C at baseline and 3rd monthx

with other OADs were analyzed. ECG pattern was recorded at baseline and at the end of 1st month and 3rd month of therapy, to determine changes in the QT interval. The average change in the mean QT interval was 0 ± 1.5 ms at the end of 1st month and 0.7 ± 0.2 ms at the end of 3rd month. No significant change in the mean QT interval at baseline and 1st month (P = 0.99) and at baseline and 3rd month (P = 0.69) was seen. Thus, 20 mg dose of teneligliptin was relatively safe in study population. A thorough QT/QTc evaluation study was also conducted by Kishimoto in Japan[9] where teneligliptin 40 and 160 mg were actively compared to moxifloxacin. Teneligliptin 40 mg/day which is currently the maximal recommended dose prolonged the QTc by 4.9 ms after 3 h. 160 mg/day of teneligliptin significantly increased the QT by 11.2 ms after 1.5 h, almost similar to 12.1 ms of QTc prolongation as observed 2 h after moxifloxacin. While teneligliptin 160 mg (although not recommended

for clinical use) is clearly associated with a prolonged QTc, teneligliptin 40 mg does not cross the critical threshold of 5 ms. The threshold for QT prolongation will become more important when teneligliptin will be prescribed with several other drugs which tend to prolong QTc including antibiotics (azithromycin), antihistaminics (astemizole and terfenadine), diuretics (thiazide), selective serotonin uptake inhibitors, haloperidol, and obviously antiarrhythmic drugs (amiodarone and sotalol).[10] Moreover, hypoglycemia being one of the strong QTc prolongation, combination with other hypoglycemic drug, may need strict pharmacovigilance.[10]

Apart from its favorable effect on QT interval, teneligliptin was also associated with significant improvement in FPG, PPG, and HbA1C at the end of 1st month and 3rd month, with average decrease in FPG, PPG, and HbA1C at the end of 3rd month as 49.6 ±32.6 mg/dl, 100.5 ± 49.4 mg/dl, and 0.9 % ± 0.4%, respectively. Similar results were reported in Treat India study,[11] where mean HbA1c, FPG, and PPG were significantly reduced by 1.37% ± 1.15%, 51.29 ± 35.41 mg/dL, and 80.89 ± 54.27 mg/dL, respectively, at the end of 3 months of teneligliptin therapy. The above results were in line with the study conducted by Chatterjee[12] where 12-week teneligliptin showed significant change in HbA1c (9.6 ± 2.1–8.4 ± 1.2%, $P < 0.001$), FPG (181.4 ± 54.5–140.9 ± 27.1 mg/dL, $P < 0.001$), and PPG (273.7 ± 75.6–201.1 ± 47.7 mg/dL, $P < 0.001$).

Our study was limited by retrospective nature and small sample size, which warrants further need of a large-scale real-world randomized trial with longer follow-up period. In addition, taking into account that there are diabetic patients who have concurrent diseases such as arrhythmia and ischemia and that teneligliptin may be administered to such patients for a long period of time, it is deemed necessary to collect information on the safety data through post-marketing surveillance study.

CONCLUSION

At therapeutic dose (20 mg once daily) usually prescribed in clinical practice, teneligliptin was not associated with significant change in QT interval and was associated with significant decrease in HbA1c, FPG, and PPG during the study period.

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Original Article

A Study of Serum Magnesium Levels in Type 2 Diabetes Mellitus

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Abstract

Background and Objectives: Magnesium deficiency is proposed as a factor in the pathogenesis of diabetic complications. Hypomagnesemia can be both a cause and a consequence of diabetic complications. The aim of our study was to know the relationship between magnesium levels and diabetes, association with level of control of diabetes, and magnesium levels in relation to complications of diabetes.

Method: This study was undertaken at MGM Hospital, Warangal from August 2014 to October 2015. A total of 75 cases of type 2 diabetes mellitus were taken for the study after satisfying the inclusion and exclusion criteria. Furthermore, 35 non-diabetic patients admitted during this period were also included in the study under the control group. All the patients were evaluated in detail, and serum magnesium levels were estimated using calmagite method.

Results: The serum magnesium levels among cases and controls were 1.88 ± 0.28 mg/dl and 2.1 ± 0.29 mg/dl, respectively. The mean serum magnesium levels in patients with controlled diabetes were 2.04 mg/dl and 1.73 mg/dl in patients with uncontrolled diabetes. Significant association was found between hypomagnesemia and diabetic retinopathy and nephropathy. There was no significant association between magnesium levels and diabetic neuropathy, ischemic heart disease, and peripheral vascular disease.

Conclusion: There was a significant reduction in serum magnesium levels in diabetics compared to the controls. There was a significant correlation between magnesium levels and level of control of diabetes. Uncontrolled diabetics had a low of serium magnesum. Low magnesium levels were mainly associated with diabetic retinopathy and nephropathy. Duration of diabetes and high levels of fasting blood sugar also had an association with low magnesium levels.

Key words: Type 2 diabetes meillitus, magnesium, Level

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems, leading to microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (coronary heart disease, peripheral arterial disease, and cerebrovascular disease).[1]

Low magnesium status has repeatedly been demonstrated in patients with type 2 diabetes. Magnesium deficiency appears to have a negative impact on glucose homeostasis and insulin sensitivity in patients with type 2 diabetes.[2]

Magnesium deficiency has been found to be associated with microvascular disease in diabetes. Hypomagnesemia has been demonstrated in patients with diabetic retinopathy, lower levels of magnesium predicting a greater risk for diabetic retinopathy, magnesium depletion has also been associated with arrhythmogenesis, vasospasm, platelet activity, and hypertension.[3] 25–39% of outpatient diabetics have low concentrations of serum magnesium,[4] and numerous studies have shown lower serum magnesium concentrations in type 2 diabetics compared to healthy controls.[5,6] The reasons why magnesium deficiency occurs in diabetes are not clear, but may include increased

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urinary loss, lower dietary intake, or impaired absorption of magnesium compared to healthy individuals.[7]

Several studies have reported increased urinary magnesium excretion in type 1 and 2 diabetes[8-11] some reporting a correlation between glycemic control and urinary magnesium loss.[10]

Magnesium is involved in insulin secretion, binding, and activity. Cellular deficiency of magnesium can alter the membrane-bound sodium-potassium-adenosine triphosphatase which is involved in maintaining the gradient of sodium and potassium and also in glucose transport.[12]

Low dietary intake may also contribute to low magnesium status in diabetics. Patients with type 2 diabetes are often overweight and may consume a diet higher in fat and lower in magnesium density than non-diabetes. However, the few studies that have reported magnesium intake in type 2 diabetes are equivocal.[6,13] Impaired intestinal absorption might also contribute to low magnesium status in diabetics. However, there are no published data on magnesium absorption in humans with diabetes. Despite the growing realization of the importance of magnesium in human health and disease, measurement of magnesium status remains problematic. Serum magnesium concentrations can be normal despite depletion of intracellular magnesium.[14]

Magnesium deficiency may result in disorders of tyrosine-kinase activity on the insulin receptor, event related to the development of post-receptoral insulin resistance and decreased cellular glucose utilization[15] that is, the lower the basal Mg, the greater the amount of insulin required to metabolize the same glucose load, indicating decreased insulin sensitivity. Experimental researches have shown that patients with diabetic retinopathy present low concentration of plasma magnesium, disposing to a higher risk of advanced retinopathy.[16]

In type 2 diabetic patients with microalbuminuria or clinical proteinuria showed a significant decrease in serum ionized Mg levels, it was also observed a significant negative correlation between serum ionized Mg and glycated hemoglobin (HbA1c) and triglycerides, in both microalbuminuria and clinical proteinuria groups.[17] In elderly type 2 diabetics, Paolisso *et al*.[18] demonstrated that oral supplementation of magnesium for 4 weeks resulted in lower fasting plasma glucose levels, increased plasma and erythrocyte magnesium levels and an increase in B-cell response to glucose.

The present study was undertaken with an aim to correlate serum magnesium levels with microvascular and macrovascular complications of diabetes- retinopathy, nephropathy, neuropathy and ischemic heart disease (IHD), and peripheral vascular disease.

Objectives

The study is aimed at:

1. Estimating fasting serum magnesium concentration in patients with type 2 DM.
2. Correlating serum magnesium concentrations with microvascular and macrovascular complications of Type 2 DM - retinopathy, nephropathy, neuropathy, IHD, and peripheral vascular disease.

PATIENTS AND METHODS

Source of Data

Patients with type 2 diabetes admitted in MGM Hospital between August 2014 and October 2015 were included in the study. Furthermore, 35 non-diabetic patients admitted during this period were also included in the study under the control group.

Method of Collection of Data

A total of 75 patients with type 2 DM and 35 controls admitted to MGM Hospital underwent the following tests:

1. Fasting blood sugar (FBS)
2. Postprandial blood glucose (measured 2 h after a standard meal)
3. Fasting serum magnesium levels (calmagite dye method), normal 1.8–2.5 mg/dl
4. 24 h urinary protein
5. Urine routine
6. Electrocardiography
7. Fundoscopy
8. RFT
9. HbA1c (immunoturbidimetric method).

Diabetics were divided into controlled (HbA1c <7) and uncontrolled (HbA1c >7).

Inclusion Criteria

All cases of type 2 DM and age- and sex-matched non-diabetic patients admitted in MGM Hospital were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. Patients with chronic renal failure
2. Acute myocardial infarction in past 6 months
3. Patients on diuretics
4. Patients receiving magnesium supplements or magnesium-containing antacids
5. Malabsorption or chronic diarrhea
6. Patients with a history of alcohol abuse
7. Pregnant women with hypertension, proteinuria, and eclampsia
8. Patients with a history of epilepsy

Estimation of Serum Magnesium

Colorimetric method using calmagite dye

Test principle

Under alkaline conditions, magnesium ions react with calmagite to produce a red complex which is measured spectrometrically at 530 mm. The intensity of the color produced indirectly proportional to the concentration of magnesium in serum. Ethylene glycol tetraacetic acid (EGTA) is included in the reagent to estimate the interference of calcium during estimation. Heavy metal interference is prevented by the presence of cyanide and a surfactant system to remove protein interference.

Kit contents

• Reagent 1: Magnesium color reagent
Calmagite 0.006w/v
Stabilizer 1% w/v
Surfactant 0.03 w/v.
• Reagent 2 Magnesium buffer reagent
2-Ethylaminoethanol 6%
EGTA 1.18 mm
Potassium cyanide 0.10%.
• Reagent 3: Magnesium standard
Magnesium salt 2 mEq/L.

Preparation of the working reagent

Ten volumes of color reagent 1 are mixed with one volume of buffer reagent (reagent 2).

Specimen

Fresh hemolyzed serum was taken, as hemolyzed sample may falsely elevate the magnesium levels.

Test procedure

In test tubes	Blank	Standard	Test
Magnesium working reagent	1.0 ml	1.0 ml	1.0 ml
Standard	-	10 µl	-
Distilled water	10 µl	-	-
Sample	-	-	10 µl

These test tubes are incubated at room temperature (22–28°C). The absorbance of test (A), Standard (As), and Blank (Ab) is read at 530nm in a spectrophotometer.

Magnesium concentration is calculated by the following formula.

Magnesium concentration (mEq/L) = (A−AB/AS−AB) × 2

Serum magnesium concentration is expressed in mg/dl by linearly of 1 mEq/L = 1.2 mg/dl.

Normal value (Adults): 1.8 mg/dl−2.5 mg/dl.

Statistical Method

Z-test has been used to find the significance of mean patter of serum magnesium between cases controls (Insulin/OHAs and controlled/uncontrolled).

ANOVA was used to find the mean pattern of serum magnesium in different complications, in a different range of FBS.

RESULTS

Study Design

A comparative study consisting of 75 diabetic patients and 35 was undertaken to investigate the change pattern of serum in DM cases when compared to controls and magnesium levels in relation to complications of DM [Table 1].

The mean age of the diabetics was 59.56 ± 9.70 and 58.66 ± 10.26 in controls 28.

Sex Distribution

Sex distribution in diabetics was male 57.33% and females 42.67% whereas in controls males 57.14% and females 42.86%. The maximum number of patients was in the age group of 51–60 years, that is, 36.0% [Table 2].

The mean FBS levels among cases and controls were 206 mg/dl and 94.86 mg/dl, respectively. Among cases, mean FBS was found to be high as compared to controls, probably due to poor diabetic control. The mean serum creatinine levels among cases and controls were 0.96 mg/dl and 0.90 mg/dl, respectively [Table 3].

The mean serum magnesium levels in cases and controls are 1.88 mh/dl and 2.1 mg/dl with a $P < 0.003$, which is

Table 1: Number of cases and controls

Age in years	Number of cases (%)	Number of controls (%)
41–50	17 (22.7)	7 (20)
51–60	27 (36.0)	13 (37.2)
61–70	23 (30.7)	11 (31.4)
71–80	7 (9.3)	3 (8.6)
80	1 (1.6)	1 (2.9)
Total	75 (1.3)	1 (2.9)
Mean±SD	59.56±9.70	58.66±10.26

Table 2: Sex distribution

Sex	Number of cases (%)	Number of controls (%)
Male	43 (57.33)	20 (57.14)
Female	32 (42.67)	15 (42.86)
Total	75 (100.0)	35 (100.0)

statistically significant. Although the exact reason is not known, this could probably be explained on the basis of increased urinary loss and low dietary patients [Table 4].

Hypomagnesemia was seen in 38.6% of the cases whereas only 2.9% of the controls had hypomagnesemia.

The mean serum magnesium levels among patients with controlled diabetes were lower as compared to patients with controlled diabetes, which was statistically significant ($P < 0.001$. Hyperglycemia directly causes suppression of magnesium.

Of the 75 diabetic patients, 33 (44%) were on OHAs, 12(16%) were on insulin alone, and 30 (40%) were on both OHAs and insulin. The mean serum magnesium levels in the OHA group, insulin group, and OHA + insulin group were 1.9 mg/dl, 1.73 mg/dl, and 1.82 mg/dl, respectively. The serum magnesium levels were significantly lower in the insulin-treated group as compared to the OHA treated group ($P = 0.013$) [Tables 5-7].

This is because insulin causes shift of magnesium from extracellular to intracellular compartment causing low serum magnesium levels.

The mean serum magnesium levels inpatients with and without diabetic nephropathy were 1.80 mg/dl and 2.09 mg/dl, respectively, which were statistically significant ($P < 0.0002$).

Table 3: Mean pattern of fasting blood sugars and serum creatinine levels

FBS/Serum creatinine Mean±SD	Cases	Controls	*P* value
FBS (mg/dl)	206.33±54.89	94.86±11.78	0.0001
Serum creatinine	0.96±0.34	0.90±0.20	0.0725

FBS: Fasting blood sugar

Table 4: Serum magnesium levels in cases and controls

Serum magnesium (*n*=1.8–2.5 mg/dl)	Cases	Controls
Range (minimum-maximum)	1.1–2.7	1.5–2.7
Mean±SD	1.88±0.28	2.1±0.29
95% CI	1.81–2.00	2.00–2.20

$P < 0.003$. CI: Confidence interval

Table 5: Comparison of serum magnesium levels between cases and controls

Serum magnesium	Cases *n*=75 (%)	Controls *n*=35 (%)
<1.8	29 (38.6)	1 (2.9)
1.8–2.5	45 (60.0)	32 (91.4)
2.5	1 (1.4)	2 (5.7)

Serum magnesium levels among patients with only one complication were 2.07mg/dl, and among them 7.2% had retinopathy, 8% had nephropathy, and 0% had neuropathy.

Mean serum magnesium levels among patients with two complications were 1.79 mg/dl and among them, 28% had retinopathy with nephropathy and 17.3% had nephropathy with neuropathy.

Among patients with all three complications, the mean serum magnesium levels were 1.74% mg/dl and were seen in 17.3% of the patients [Tables 8 and 9].

DISCUSSION

The present study included 75 diabetic patients (cases) and 35 non-diabetic patients (controls). Serum magnesium levels were determined in all the subjects.

The present study has diabetic patients ranging from 41 to 80 years of age. The mean age in cases and controls was 59.56 years and 58.66 years, respectively. Male patients in cases and controls were 57.33% and 57.14%, respectively, and females were 42.67% and 42.86%, respectively.

In this study, mean serum magnesium levels in cases and controls were 1.88 ± 0.28 mg/dl and 2.10 ± 0.29 mg/dl, respectively, which means diabetics are having low serum magnesium level compared to non-diabetics, with a $P < 0.003$ which is statistically significant.

Table 6: Effect of level of control of DM on serum magnesium

Serum magnesium	Controlled (*n*=37)	Uncontrolled (*n*=38)
Range (minimum-maximum)	1.5–2.7	1.1–2.1
Mean±SD	2.04±0.29	1.73±0.23
95% CI	1.94–2.13	1.65–1.81

$P = 0.001$. CI: Confidence interval, DM: Diabetes mellitus

Table 7: Effect of the type of treatment on serum magnesium

Serum magnesium	Insulin (*n*=12)	OHAs (*n*=33)
Mean (minimum-maximum)	1.4–2.0	1.5–2.4
Mean±SD	1.72±0.22	1.99±0.31
95% CI	1.58–1.87	1.88–2.10

$P = 0.013$. CI: Confidence interval

Table 8: Serum magnesium levels in patients with diabetic nephropathy

Serum magnesium	Microalbuminuria	Macroalbuminuria
Mean±SD	1.86±0.29	1.67±0.20

In the present study, patients with controlled sugars have a mean serum magnesium levels of 2.04 ± 0.29 mg/dl and patients with uncontrolled sugars have a mean of 1.73 ± 0.23 mg/dl, which is consistent with the study done by Jain *et al.* had a mean serum magnesium of 1.85 ± 0.08 mg/dl in patients with controlled diabetes and 1.68 ± 0.12 mg/dl in uncontrolled diabetes. On establishing, the relationship between magnesium levels and the state of control of diabetes. It was observed that in poorly controlled DM serum magnesium levels were lower than in those whose diabetes was fairly controlled.

In the present study, patients treated with insulin had lower serum magnesium levels as compared to those treated without insulin (1.73 ± 0.22 mg/dl vs. 1.99 ± 0.31 mg/dl). Yajnik *et al.* reported that insulin-treated diabetics have significantly lower serum magnesium levels as compared to non-insulin-treated diabetics. In another study done by Jain *et al.* also found that patients getting insulin therapy had low serum magnesium than those getting OHAs (1.59 ± 0.13 mg/dl vs. 1.90 ± 0.18 mg/dl). In a study done by Alzaida *et al.*, they found that cellular uptake of magnesium in normally stimulated by insulin. Hence, insulin treatment may enhance cellular magnesium uptake and result in increased prevalence of hypomagnesemia. Earlier studies have shown that sex, age, and duration of diabetes were not a significant predictor of serum magnesium levels. Later Yajnick *et al.* reported that among diabetics plasma magnesium concentration was directly related to age and sex among the men had significantly higher concentration than women, the increasing magnesium levels with age were probably due to impaired renal function and the sample size (87 diabetics and 30 non diabetics) was relatively small to confirm male preponderance.

In this study, patients with impaired renal function were excluded. Our results confirmed the recent reports that have not shown any significant association between sex and age, but the duration of diabetes had a relation with serum magnesium levels, patients with duration of diabetes >5 years had lower serum magnesium levels as compared to those with a duration of diabetes <5 years.

Previously magnesium deficiency has been found to be associated with diabetic microvascular complications. In the present study also, significantly lower levels of serum magnesium were observed in diabetics with microvascular complications [Tables 10 and 11].

Hypomagnesemia has been reported in patients with diabetic retinopathy with lower serum magnesium levels predicting a greater risk of severe diabetic retinopathy.

Table 9: Complications

Serum magnesium	One complication (*n*=25)	Two complications	All three (*n*=13)
Mean±SD	2.07±0.30	1.79±0.25	1.74±0.29
95% CI	1.94–2.19	1.70–1.88	1.56–1.92

CI: Confidence interval

Table 10: Serum magnesium levels in controlled and uncontrolled diabetes

Serum magnesium levels Mean±SD	Controlled diabetes	Uncontrolled diabetes
Jain *et al.*	1.85±0.08	1.68±0.12
Present study	2.04±0.29	1.73±0.23

Table 11: Serum magnesium levels in patients on insulin and OHAs

Serum magnesium Mean±SD	Insulin	OHAs
Jain *et al.*	1.59±0.13	1.90±0.18
Present study	1.73±0.22	1.99±0.31

Kundu *et al.* (2013) compared 30 type 2 diabetic patients without retinopathy. 30 type 2 diabetic patients with retinopathy in the age group 45–75 years as cases and 60 age- and sex-matched healthy individuals as controls. Hypomagnesemia was observed in cases with type 2 diabetic patients without retinopathy (2.02 ± +0.29) and in type 2 diabetic patients with retinopathy (1.38 ± 0.39) when compared with controls (2.62 ± 0.36). The results were comparable with the present study. The present study revealed a definite association between diabetic retinopathy and low serum magnesium levels. Patients with diabetic retinopathy and those without it had a mean serum magnesium level of 1.76 mg/dl and 2.01 mg/dl, respectively. These observations are similar to other reports.

The mechanism by which hypomagnesemia predisposes to retinopathy is not clear. Grfton *et al.* have proposed the inositol transport theory to explain this association. However, the exact reason remains obscure.

Patients with nephropathy had a significant association with hypomagnesemia. Patients with microalbuminuria and macroalbuminuria had a mean serum magnesium level of 1.86 ± 0.29 mg/dl and 1.67 ± 0.20 mg/dl, respectively, indicating that patients with macroalbuminuria had a lower serum magnesium levels as compared to patients with microalbuminuria.

In a study done by Kareem *et al.* found that patients with diabetic retinopathy showed a significant rise in serum cholesterol and triglyceride. Hence, they stated that

probably hypomagnesemia and increased serum cholesterol and triglyceride levels are responsible for microvascular changes in diabetes leading to retinopathy.

There was no association seen with magnesium levels in patients with neuropathy. There was a correlation between serum magnesium levels and the number of complications. Patients with only one complication had a mean serum magnesium level of 2.07 ± 0.03 mg/dl, and patients with two complications had a mean of 1.79 ± 0.25 mg/dl and those with three complications had a mean of 1.74 ± 0.29 mg/dl. Patients with more than one complication had much lower serum magnesium levels indicating more the complications lesser the magnesium levels.

Nadler and Rude[4] evaluated intracellular (erythrocytic) Mg^2 concentration in 20 type 2 diabetic patients. In addition, the effects of intravenous 3-h drip or 8 weeks of oral magnesium supplementation on intracellular Mg^2 concentration levels and platelet reactivity were studied. The results showed that the intracellular Mg^2 concentration of diabetic patients was reduced compared to non-diabetics.

However, the present study did not include evaluating the effects of oral or iv magnesium supplementation.

There was no scope for follow-up in the present study. Hence, the change in magnesium states with respect to improvement or worsening of diabetic state, in the long run, was not studied. This study focuses on estimating magnesium levels in type 2 diabetics at a given point (during admission) but not on therapeutically correcting hypomagnesemia or otherwise (not correcting) in the future course of the disease and its outcome.

CONCLUSION

1. Serum magnesium levels were low in type 2 diabetics when compared to controls.
2. Levels of serum magnesium were further lower in uncontrolled type 2 diabetics than those in whom diabetes was controlled.
3. Hypomagnesemia was associated with diabetic retinopathy and diabetic nephropathy.
4. No correlation was found in respect to neuropathy and IHD.
5. More the duration of diabetes and the levels of FBS, lower was the serum magnesium levels.
6. Patients on insulin had lower levels of serum magnesium as compared to patients on OHAs.
7. Hypomagnesemia is a factor in type 2 diabetes and associated with various complications. Hence, it is worth measuring serum magnesium levels in patients with type DM and probably correlate their relationship with various complications.

SUMMARY

Estimation of serum magnesium levels of 75 diabetic patients and 35 controls admitted to MGM Hospital.

1. The mean serum magnesium levels were 1.88 mg/dl and 2.1 mg/dl in cases and controls, respectively.
2. Most admissions were due to various infections followed by cardiovascular problems. Peripherals vascular disease, neurological problems, and poorly controlled diabetes.
3. The mean serum magnesium levels in patients on insulin, OHAs, and OHAs plus insulin were 1.72 mg/dl, 1.99 mg/dl, and 1.82 mg/dl, respectively.
4. The mean serum magnesium levels in patients with controlled diabetes were 2.04 mg/dl and 1.73 mg/dl in patients with uncontrolled diabetes.
5. The mean serum magnesium levels in patients with and without diabetic retinopathy were 1.77 mg/dl and 2.01 mg/dl, respectively.
6. Whereas the mean serum magnesium levels in patients with diabetic nephropathy were 1.80 mg/dl and 2.09 mg/dl in those without nephropathy.

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Original Article

A Study on Clinical and Etiological Factors of New-Onset Seizures in Adults

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Abstract

Introduction: Seizure has been recognized since antiquity and probably as old as man himself. Seizures are common disorders found all over the world and are encountered frequently during medical practice in variety of settings.

Materials and Methods: Patients presenting with a history of seizures were included in the study. Patient and eyewitness were interviewed regarding history, and clinical examination was done as mentioned in pro forma.

Conclusion: Seizure being a medical emergency, its etiological determination is quite important in expediting the management and helping in the prevention of seizures. Etiological spectrums of seizures vary from region to region which includes neuroinfection, CVA, tumor, metabolic, poisoning, and alcohol withdrawal.

Key words: Focal, Hypoglycemia, Seizures

INTRODUCTION

Seizure has been recognized since antiquity and probably as old as man himself. Seizures are common disorders found all over the world and are encountered frequently during medical practice in variety of settings. Although a variety of factors influence the incidence and prevalence of seizures, 5–10% of the population will have at least one seizure, with the highest incidence occurring in early childhood and late adulthood.[1]

Etiological spectrum of acute symptomatic seizures in developing countries is different from developed countries. At present, central nervous system (CNS) infections such as malaria, meningitis, tuberculosis, HIV, and neurocysticercosis account for significant number of cases in developing countries.[2] Since these infections vary from region to region, etiology of seizure may also vary from region to region.

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Single small enhancing computed tomography lesions (SSECTLs) (ring enhancing/disc lesions, 20 mm in size) are an important cause of seizures in India. Initially, it was thought that SSECTLs were due to tuberculosis, focal encephalitis, microabscesses, and cysticercosis, but now, histopathological studies suggest that in most of the cases, SSECTL is due to dying cysticercus larva.[3] Hence, etiology itself changes over time.

In Indian subcontinent, cerebral venous thrombosis is common in post-puerperal women presents with severe headache, low-grade fever, and seizures.[4] Focal seizures are more common, but they can generalize to a life-threatening status epilepticus.[5]

Etiology of seizures can be easily made out in most of the older patients. The causes include subdural hematoma, stroke, CNS infections, and degenerative disorders such as Alzheimer's disease and malignancy which includes malignant gliomas and brain metastases.[6] In stroke, seizures occur more commonly with hemorrhagic stroke than with ischemic stroke. They also can occur with systemic metabolic conditions such as uremia, hyperglycemia, hypoglycemia, hyponatremia, and alcohol withdrawal.[6]

Seizures can be presenting feature in tubercular meningitis, which is the most common type of chronic meningitis in

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India. >60% of patients with intracranial tuberculoma may have seizures.[2]

Hence, this study is done to know the various etiologies of new-onset seizures in adults in this region.

With the advent of modern technologies such as CT scan, magnetic resonance imaging, and cerebrospinal fluid serology for infection such as viral, tubercular, and neurocysticercosis, the diagnosis of seizure has become more accurate and has completely changed the course of management.

Aims of Study

The aims of this study were as follows:

1. To study the clinical and etiological factors of new-onset seizures in patients of Mahatma Gandhi Memorial Hospital, Warangal, located in Northern Telangana which is a tertiary hospital for four districts, that is, Warangal, Karimnagar, Khammam, and Nalgonda constituting urban, rural, and tribal areas.
2. Number of patients considered: 100.

Objective of Study

The objective of this study was to evaluate the cause for new-onset seizures in 100 number of adult inpatients admitted at Mahatma Gandhi Memorial Hospital, Warangal.

MATERIALS AND METHODS

Type of Study

This is a prospective and observational study.

Source of Data

A total of 100 patients admitted with new-onset seizures from the Mahatma Gandhi Memorial hospital attached to Kakatiya Medical College, Warangal, who fulfilled the inclusion and exclusion criteria as mentioned below.

Duration of Study

The study began on January 2016 and ended on October 2017.

Methods of the Collection of Data

Patients presenting with a history of seizures were included in the study. Patient and eyewitness were interviewed regarding history, and clinical examination was done as mentioned in pro forma.

Inclusion Criteria

The following criteria were included in the study:

1. Age of patients more than or equal to 15 years.
2. Patients presenting with new-onset seizures.

New-onset seizure is defined as the first seizure (or the first cluster of seizures within 24 h period) ever experienced by the patient.

Exclusion Criteria

The following criteria were excluded from the study:

- Patient with seizure-like episodes,
- Patients who are known epileptics,
- Patients with a history of drug non-compliance of automated external defibrillators, hyperventilation, TIA, narcolepsy, and movement disorder such as choreoathetosis, tic disorder, and psychogenic seizures,
- Patients not willing to participate in this study.

RESULTS AND OBSERVATIONS

The results of the study are shown in Tables 1-4. Number of cases of the new-onset seizures studied - 100.

In the present study, patient's age ranged from 15 years to 74 years, with mean of 40.51 years. Majority of patients were in the age group of 21–30 years (n = 29, 29%) followed by 41–50 years (n = 19, 19%). 75% of the patients were in the 2nd–5th decades. 6% of the patients were in the age group of >60 years. Least number of patients are seen in age group >70. Of 100 patients, 56 were male and 44

Table 1: Age and sex distribution

Age in years	Male	Female	Combined
	n (%)	*n* (%)	*n* (%)
≤20	6 (10.7)	3 (6)	9 (9)
21–30	15 (26.8)	14 (31.8)	29 (29)
31–40	11 (19.6)	7 (15.9)	18 (18)
41–50	10 (17.8)	9 (20.45)	19 (19)
51–60	9 (16.1)	8 (18.18)	17 (17)
61–70	4 (7.1)	2 (4.5)	6 (6)
>70	1 (1.7)	1 (2.2)	2 (2)
Total	56 (56)	44 (44)	100 (100)
Mean±SD	44.84±16.15	35.22±15.33	40.51±16.42

Table 2: Etiologies according to sex distribution

Etiology	Male (*n*=56)	Female (*n*=44)	Combined (*n*=100)
	n (%)	*n* (%)	*n* (%)
Neuroinfection	20 (57)	15 (43)	35 (35)
Cerebrovascular accidents	16 (55)	13 (45)	29 (29)
Metabolic	4 (40)	6 (60)	10 (10)
Idiopathic	4 (57)	3 (43)	7 (7)
Alcohol related	6 (100)	0 (0)	6 (6)
Poisoning	3 (60)	2 (40)	5 (5)
Tumor	3 (75)	1 (25)	4 (4)
Eclampsia	0 (0)	3 (100)	3 (3)
Miscellaneous	1(100)	0 (0)	1 (1)

Table 3: Correlation of etiologies with age group

Etiology	Age in years							Total
	15–20	21–30	31–40	41–50	51–60	61–70	>70	
Neuroinfection	4	14	10	5	2	0	0	35
Cerebrovascular accidents	0	4	3	7	9	5	1	29
Metabolic	1	1	1	5	2	0	0	10
Idiopathic	2	4	1	0	0	0	0	7
Alcohol related	0	0	2	1	2	1	0	6
Poisoning	2	3	0	0	0	0	0	5
Tumor	0	1	0	1	1	0	1	4
Eclampsia	0	2	1	0	0	0	0	3
Miscellaneous	0	0	0	0	1	0	0	1
Total	9	29	18	19	17	6	2	100

Table 4: Etiological spectrum of seizures

Paramters	Sander *et al.*[14] (1990) (%)	Present study (%)
Acute symptomatic seizures	15	89
Idiopathic seizures	62	7
Remote symptomatic seizures	21	4 (post-infarct)

were female, with male-to-female ratio of 1.26:1.0. Majority of males and females were in the 3rd decade.

Neuroinfection is a leading cause of seizure, which accounted for 35% followed by cerebrovascular accidents (29%) and metabolic (10%). In 7% of patients cause is idiopathic (cryptogenic). Alcohol related is 6%, poisoning 5%, tumor 4%, eclampsia related 3%, and post-dialysis 1%.

Among neuroinfection (n = 35), majority of seizures were due to neurocysticercosis accounted for 34% followed by meningitis 31% and cerebral malaria 21%. 12% of seizures were due to neurocysticercosis, of which SSECTL was seen in 42%[5] of NCC patients, multiple healed calcified granulomas in 42%[5] of patients, and multiple ring-enhancing lesions in 16%[2] of patients. 15% of seizures were due to CNS tuberculosis. Meningitis accounted for 46.6% followed by tuberculoma 26.6%[4] and meningoencephalitis 26.6%.[4]

Meningitis accounted for 15% (n = 15) of seizures. Tubercular meningitis is the most common meningitis (n = 9, 60%) followed by viral 26.6%[4] and bacterial 13.3%.[2]

Among cerebrovascular accidents (n = 29), stroke accounted for 82% (infarct - 14 and hemorrhage - 10) followed by cerebral venous thrombosis 13%[4] and subarachnoid hemorrhage 1%.

In metabolic seizures (n = 10), 50% were due to hypoglycemia.[5] 5% of cases are poison related, 4% of cases are tumor related, and 7% of cases are idiopathic.

7% of seizures were pregnancy related. (CVT-4 + Eclampsia-3). 6% of cases are alcohol related.

In males (n = 56), 35.7% of males had seizures due to neuroinfection. 28.5% of males had seizures due to CVA. 10.7% of males had seizures due to alcohol-related products. 7.1% of males had seizures due to idiopathic cause 7.1% of males had seizures due to metabolic causes. 5.3% of males had seizures due to tumors. 5.3% of males had seizures due to poisoning. Among neuroinfection in males (n = 20), majority of seizures due to neurocysticercosis 35% followed by meningitis[6] and cerebral malaria.[5] Among CVA in males (n = 16), majority of seizures were due to infarct 50% followed by hemorrhage 37.5%.[6] Among metabolic (n = 4), majority are due to hypoglycemia.[3] In females (n = 44), majority of seizures were due to neuroinfection 34%, followed by CVA 29.5%, metabolic 13.6%,[6] eclampsia 6.8%,[3] idiopathic 6.8%,[3] poisoning 4.5%,[2] and tumors 2.2%.[1]

Among neuroinfection in females (n = 15), majority of seizures due to neurocysticercosis 34%[5] followed by meningitis[4] and cerebral malaria.[3] Among CVA (n = 13), majority of seizures were due to infarct 46.1%[6] followed by hemorrhage 30.7%[4] and CVT 23%.[3] All the seizures due to CVT occurred in females, and all were postpartum.

Three cases of pregnancy-related complications like eclampsia causing seizures are seen.

No cases of alcohol-related seizures are seen in females in this study.

GTCS: Generalized tonic-clonic seizures. FWA: Focal seizures with awareness. FWIA: Focal seizures with impaired awareness. SE: Status epilepticus. GA: Generalized absence.

GTCS (n = 59) is the most common seizure. The M.C cause for GTCS is neuroinfection (38.9%) followed by CVA (28.8%) and metabolic (6.7%). 35% of FWA is caused by neuroinfection followed by CVA 25%. 55.5% of FWIA

seizures due to CVA followed by neuroinfection (28.5%). 28.5% of SE seizures due to neuroinfection. One patient had FWA due to hypocalcemia. Most of neuroinfection patients presented with GTCS (65.7%). 58.6% of CVA patients presented with GTCS followed by FWA (17.2%). 40% of metabolic seizures were GTCS. 40% of patients of poisoning presented with GTCS. 42.8% of idiopathic seizures were GTCS.

DISCUSSION

Seizures are common disorders found all over the world and are encountered frequently during medical practice in variety of settings. At present, CNS infections such as malaria, meningitis, tuberculosis, HIV, and neurocysticercosis account for significant number of cases in developing countries. Since these infections vary from region to region, etiology of seizure may also vary from region to region. In Indian subcontinent, cerebral venous thrombosis is common in post-puerperal women presents with severe headache, low-grade fever, and seizures. SSECTLs are frequently reported from India. Etiological spectrum of seizures in developing countries is different from developed countries.

Hence, this study on "seizures" was done to know the various etiologies of new-onset seizures in adults in this region. The present study "The clinical and etiological study of new-onset seizures in adults" was carried out in the Mahatma Gandhi Memorial Hospital, Warangal, attached to Kakatiya Medical College, Warangal. 100 cases of new-onset seizures were selected as per the criteria mentioned in the materials and methods. The observations are compared with the studies done by others on the same subject.

Age and Sex Distribution

Etiological spectrum depends on age, sex, geography, and medical setting. Of 100 patients, 56 were male and 44 were female, with male-to-female ratio of 1.26:1.0.

Majority of males and females were in the 3rd decade.

The present study included 100 patients with new-onset seizures as per the criteria mentioned in the materials and methods.

Etiological spectrum depends on age, sex, geography, and medical setting.

In the present study, of 100 patients, 9% of patients were in the age group of 15–19 years, 47% of patients were in the age group of 20–39 years, 36% of patients were in the age group of 40–59 years, and 8% were in the age group of 60 years and above.

The major etiology for seizures seen in the 2nd and 3rd decades was neuroinfections up to 68% and metabolic seizures 50% in the 5th decade. CVA 55% in the 5th and 6th decades, poisonings 60% common in the 2nd decade, and 75% of cerebral sinovenous thrombosis occurred in the 2nd decade.

In a study from the United Kingdom by Sande *et al.* (1990), 25% were below the age of 15 years, 51% in the 3rd–4th decades, and 24% >60 years. Another study from South India (Hyderabad) by Narayanan and Murthy (2007), 36% were >60 years, with mean age of 49 years.

In the present study [Table 4], patient's age ranged from 15 years to 74 years, with mean of 40.51 years. Patients more than or equal to 15 years were included in the study. Majority of patients were in the age group of 21–30 years (n = 29, 29%) followed by 41–50 years (n = 19, 19%). 78% of the patients were in the age group of 21–60 years. 8% of the patients were in the age group of >60 years. In our study, majority of patients were younger unlike western studies are in older age group.

Mean age was lower (41 years) when compared with the study by Narayanan and Murthy, probably etiological spectrum varies from region to region. All studies were slightly male predominate.

Etiological Spectrum of Seizures

In 15% of cases, acute symptomatic seizures are seen in Sander *et al.* study. In the present study, it is 89%. Idiopathic seizures are 89% in Sander *et al.* study. In the present study, it is 7%. Remote symptomatic seizures are 21% in Sander *et al.* study. In the present study, it is 4%. Other etiologies in the present study are neuroinfection 35%, CVA 29%, metabolic 10%, idiopathic 7%, alcohol related 6%, poisoning 5%, tumor 4%, eclampsia related 4%, and post-dialysis 1%. Idiopathic seizures were the most common seizures in western population unlike acute symptomatic, in the present study, of which neuroinfections are more common.

Etiologies Observed in Various Studies

In the present study [Tables 5-9], neuroinfection is a leading cause of seizure which accounted for 35% followed by cerebrovascular accidents 29% and metabolic 10%. In 7% of patients cause is idiopathic (cryptogenic). Majority of seizures were due to neurocysticercosis accounted for 34% followed by meningitis 31% and cerebral malaria 21%.

Stroke accounted for 82% (infarct - 14 and hemorrhage - 10) followed by cerebral venous thrombosis 13%.[4] 7% of seizures were pregnancy related. (CVT-4 + Eclampsia-3). In metabolic seizures (n = 10), 50% were due to hypoglycemia.[5]

Neuroinfection occurred in 2% of the patients in Sander *et al.*[14] study, 15% in Hauser *et al.*, 77% in the study by Murthy and Yangala,[2] and 32% in a study by Narayanan and Murthy. In our study, etiology is comparable to Indian studies.

SSECTLs (ring enhancing/disc lesions, 20 mm in size) are an important cause of seizures in India. SSECTL accounted for 50% of seizures in a study by Murthy and Yangala.[2] In our study, it occurred only in 5% of cases [Table 6]. This may be due to regional variation in incidence of neurocysticercosis.

CVA occurred in 15% of the patients in Sander *et al.*study, 18% in Hauser *et al.*, 14% in the study by Murthy and Yangala,[2] and 21% in a study by Narayanan and Murthy. In our study, CVA occurred in 29%. This is because ischemic was seen in 14% of cases.

Alcohol-related seizures occurred in 9% of the patients in Sander *et al.* study, 11% in Hauser *et al.*, and 6% in our study. Alcohol-related seizures were less common when compared with western studies. Seizures due to alcohol withdrawal were more common than poisoning in the present study. In our study [Table 10],

Table 5: Sander *et al.* (1990) (UK)

Paramters	Percentage (%)
Vascular	15
Tumor	6
Infection	2
Alcohol related	9

Table 6: Murthy and Yangala (1999) (Hyderabad)[2]

Paramters	Percentage (%)
Neuroinfection	77
Neurocysticercosis	20
CNS tuberculosis	16
Vascular	14
Stroke	11
CVT	3
Metabolic	3
Tumors	7

Table 7: Narayanan and Murthy (2007)

Paramters	Percentage (%)
Neuroinfection	32
Neurocysticercosis	13
Tuberculoma	4.5
Vascular	21
Stroke	18
CVT	3
Metabolic	32
Others	15
Alcohol	9

- 68% of neuroinfection were seen in the 3rd and 4th decades
- 31.1% occurred in the 6th decade, 24.1% of CVA occurred in the 5th decade.
- 51.7% of stroke occurred after 50 years.
- 50% of metabolic seizures occurred in the 5th decade.

Etiological spectrum of seizures in different age group was significantly different in our study when compared to Hauser *et al.* study. Seizures due to neuroinfection were leading cause in the age group of 15–35 years and 35–64 years in our study, whereas alcohol-related seizure in Hauser *et al.* study.

- 40% of metabolic seizures were GTCS.
- 40% of patients of poisoning presented with GTCS.
- 42.8% of idiopathic seizures were GTCS.

One case of FWA due to hypocalcemia occurred in our study.

Table 8: Etiological spectrum of seizures in different age group

Paramters	Hauser *et al.*[13] study (1995) (U.S.A)	Our study
15–35 years	Alcohol related (11%) Head trauma (8%)	Neuroinfection (28%) CVA (7%)
35–64 years	Alcohol related Tumor (13%) Head trauma (5%) Stroke (20%)	Neuroinfection (7%) Stroke (20%) Idiopathic (7%) Alcohol related (6%) Poisoning (5%)
>65 years	Stroke (50%)	CVA (5%)

Table 9: Different types of seizures in various studies

Paramters	Generalized tonic-clonic (%)	Focal with awareness (%)
Sander *et al.*[14]	39	52
Murthy and Yangala[2]	22	78
Narayanan and Murthy	55	45
Our study	59	20

Table 10: Present study

Paramters	Percentage (%)
Neuroinfection	35
Cerebrovascular accidents	29
Metabolic	10
Idiopathic	7
Alcohol related	6
Poisoning	5
Tumor	4
Eclampsia	3
Miscellaneous	1

SE occurred in 3% of patient in a study by Murthy and Yangala[2] and 10% in a study by Narayanan and Murthy. In our study, etiology 7% had SE.

- 35% of patients had neuroinfection-related seizures
- 29% of patients had cerebrovascular accidents related
- 10% of patients had metabolic
- 7% of patients had idiopathic
- 6% of patients had alcohol related
- 5% of patients had poisoning
- 4% of patients had tumor
- 3% of patients had eclampsia-related seizures
- 1% of patients had due to post-dialysis.

In the present study, metabolic abnormality 40% presented as generalized tonic-clonic, 30% as FWA, and 20% as SE. In a study by Murthy and Yangala,[2], all were (100%) focal to bilateral tonic-clonic.

CONCLUSION

Seizure being a medical emergency, its etiological determination is quite important in expediting the management and helping in the prevention of seizures. Etiological spectrums of seizures vary from region to region which includes neuroinfection, CVA, tumor, metabolic, poisoning, and alcohol withdrawal. Neuroinfection and cerebrovascular accidents accounted for significant number of seizures in all the age groups. Neurocysticercosis is the most common etiology among neuroinfections in new-onset seizures.

Management of seizure is always multimodal which constitutes the treatment of underlying etiology, avoidance of precipitating factors, suppression of recurrent seizures by prophylactic therapy, and addressing a variety of psychological and social issues.

From the present study, on clinical and etiological features of new-onset seizures, the following conclusions were made.

- 93% of seizures were acute symptomatic seizures in which underlying etiologies can be made.
- Majority of seizures occurred in patients <50 years.
- Etiological spectrum of seizures was varied and included neuroinfection, CVA, tumor, metabolic, poisoning, and alcohol withdrawal.
- Neuroinfection and cerebrovascular accidents accounted for significant number of seizures in all the age groups.
- Neurocysticercosis is the most common cause in neuroinfection.
- Cerebral venous thrombosis is an important cause of acute symptomatic seizures among young patients with cerebrovascular diseases.

Summary

This prospective study was done in the MGM Hospital attached to Kakatiya Medical College, Warangal, to know the various etiologies. 100 cases of new-onset seizures who fulfilled the criteria as mentioned in materials and methods were included in the study. Of 100 patients, 56% were male and 44% were female with male-to-female ratio of 1.26:1.0. Majority of males and females were in the 3rd decade. Patient's age ranged from 15 years to 74 years, with mean of 40.51 years, with 75% of the patients were in the <50 years.

Neuroinfection was the leading cause of seizure which accounted for 35% followed by cerebrovascular accidents (29%) and metabolic (10%). In 7% of seizures were idiopathic (cryptogenic). Neurocysticercosis (35%) was the most common cause among neuroinfection followed by meningitis (37.9%) and cerebral malaria (22.8%). 82% of the CVA were due to stroke and 13.7% due to CVT. 50% of metabolic seizures were due to hypoglycemia. 7% of seizures were pregnancy related. In males, majority of seizures were due to neuroinfection (35.7%) followed by CVA (28.5%). Most of idiopathic seizures (57.1%) and all alcohol-related seizures occurred in males. In females, majority of seizures were due to neuroinfection (34%) followed by neuroinfection 28.9%. 6% of seizures were pregnancy related.

Up to the 5th decade, neuroinfection was the most common cause for seizures (33%) followed by CVA (14%). Above 50 years, CVA was the most common cause (15%) followed by metabolic seizures (2%). All CVAs occurring in the 2nd and 3rd decades in females were CVT[4] and eclampsia.[3] GTCS was the most common seizure. The most common causes for GTCS were neuroinfection (23%) followed by CVA (17%) and metabolic (4%). 35% of FWA is caused by CVA. 28.5% of SE is caused by metabolic. One patient had FWA due to hypocalcemia. 5% of seizures were GA.

The results of the present study were comparable with studies by Murthy and Yangala[2] and Narayanan and Murthy.

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Review Article

Dental Management of Children with Special Health Care Needs

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Abstract

The management of children with health care needs creates hesitation and anxiety among health professionals including dentists. There has been general agreement that disabled population has a higher prevalence of dental caries, poor oral hygiene, and compromised gingival and periodontal health than healthy population. Oral healthcare professionals require specialized knowledge acquired through special training and increased awareness. The purpose of this article is to describe the characteristics of some common developmental disabilities and medically compromised states and the challenges of these issues present to the oral healthcare professionals.

Keywords: Special health care needs(SHCN), Dental home, Behaviour guidance

INTRODUCTION

As we know every child is unique. Children cannot independently meet their social and cultural exceptions because they are emotionally and physically immature. According to AAPD Special Health Care Needs (SHCN) as "any physical, developmental, mental, sensory, behavioral, cognitive, or emotional impairment or limiting condition that requires medical management, health care intervention, and/or use of specialized services or programs. The condition may be congenital, developmental, or acquired through disease, trauma, or environmental cause and may impose limitations in performing daily self-maintenance activities or substantial limitations in a major life activity. Health care for individuals with special needs requires specialized knowledge acquired by additional training, as well as increased awareness, attention, adaptation, and accommodative measures beyond what are considered routine.[1]

The number of adolescents and youth with disabilities particularly in developing countries is significantly higher and is on the rise.[2] From several studies, we can see individuals with SHCN may be at a higher risk for dental and oral diseases compared to others.[3-5] Oral and dental diseases, which are mainly due to effects of the conditions and also the lack of dental care, can have a direct and distressing impact on the quality of life of SHCN and their families.[6] Patients with mental, developmental, or physical disabilities who do not have the ability to understand, assume responsibility for, or cooperate with preventive oral health practices are also at greater risk of oral and dental diseases. Oral health is considered an intimate part of general health and well-being.[7]

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RECOMMENDATIONS

Dental Home

In dental home, patients with SHCN are more likely to receive appropriate preventive and routine care.[8] The dental home provides an opportunity to implement individualized preventive oral health practices and reduces the child's risk of preventable dental/oral disease.

Oral health care needs may extend beyond the scope of the pediatric dentist's training when patients with SHCN reach adulthood. It is important to educate and prepare the patient and parent on the value of transitioning to a dentist who is knowledgeable in adult oral health needs. At a time

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agreed on by the patient, parent, and pediatric dentist, the patient should be transitioned to a dentist knowledgeable and comfortable with managing that patient's specific health care needs. In cases where this is not possible or desired, the dental home can remain with the pediatric dentist and appropriate referrals for specialized dental care should be recommended when needed.[9]

Scheduling Appointments

Initial contact with the dental practice allows both parent and patient an opportunity to address the child's primary oral health needs and to confirm the appropriateness of scheduling an appointment with that particular practitioner. Along with the child's name, age, and chief complaint, the receptionist should determine the presence and nature of any SHCN. The office staff, under the guidance of the dentist, should determine the need for an increased length of appointment and/or additional auxiliary staff to accommodate the patient in an effective and efficient manner. The need for increased dentist and team time as well as customized services should be documented, so the office staff is prepared to accommodate the patient's unique circumstances at each subsequent visit.[10]

It is important that the dentist be familiar and complies with Health Insurance Portability and Accountability Act (HIPAA) and AwDA regu-lations applicable to dental practices

when scheduling patients with SHCN. HIPAA insures that the patient's privacy is protected and AwDA prevents discrimination on the basis of a disability.[11]

Patient Assessment

The patient's medical history should be familiar and it decreases the risk of aggravating a medical condition while rendering dental care. Up-to-date, an accurate, comprehensive medical history is necessary for correct diagnosis and effective treatment planning. Information regarding the chief complaint, history of present illness, medical conditions, illnesses, hospitalizations, surgeries, anesthetic experiences, current medications, immunization status, allergies, review of systems, family and social histories, and thorough dental history should be obtained.[12] The dentist should include condition like sensory issues during the history intake and be prepared to modify the traditional delivery of dental care to address the child's unique needs. Consultation with the caregiver or with the patient's physician may be required, if the patient/parent is unable to provide accurate information.

The history should be consulted and updated, during every visit. Recent medical attention for illness or injury, newly diagnosed medical conditions, and changes in medications should be documented. Significant medical conditions should be identified in a conspicuous yet confidential manner in the patient's record.

Comprehensive examination of the head, neck, and oral should be completed on all patients. A caries-risk assessment should be performed.[13] Caries-risk assessment provides a means of classifying caries risk at a point in time, and therefore, should be applied periodically to assess changes in an individual's risk status. An individualized preventive program, including a dental recall schedule, should be recommended after evaluation of the patient's caries risk, oral health needs, and abilities.

A summary of the oral findings and specific treatment recommendations should be provided to the patient, parent, and caregiver, and the patient's other care providers should be informed.

Patient Communication

An attempt should be made to communicate the patient directly. Dental staff may need to communicate in a variety of non-traditional ways. A parent, family member, or caretaker may need to be present.[14,15]

Medical Consultations

The dentist should coordinate care through consultation with the patient's other care providers. When appropriate, the physician should be consulted regarding medications, sedation, general anesthesia, and special restrictions or preparations that may be required to ensure the safe delivery of oral health care. The dentist and staff always should be prepared to manage a medical emergency.[14,15]

Informed Consent

Informed consent for dental treatment must be signed by all patients. Informed consent should comply with state laws, and when applicable, institutional requirements. Informed consent should be well documented in the dental record through a signed and witnessed form.[14]

Behavior Guidance

Dental anxiety or a lack of understanding of dental care, children with disabilities may exhibit resistant behaviors, and it is challenging. These behaviors can interfere with the safe delivery of dental treatment. The parent or caregiver's assistance may need to manage patients with physical and mental disabilities in the dental office. When traditional behavior guidance techniques are not adequate, protective stabilization can be helpful in patients. Sedation or general anesthesia is the behavioral guidance armamentarium of choice when protective stabilization is not feasible or effective. An

outpatient surgical care facility might be necessary when in-office sedation or general anesthesia is not feasible or effective.[16]

Preventive Strategies

Oral diseases jeopardize the patient's health and individuals with SHCN may be at increased risk for oral diseases.[1] Education of parents and caregivers is critical for ensuring appropriate and regular supervision of daily oral hygiene. The team of dental professionals should develop an individualized oral hygiene program that takes into account the unique disability of the patient. Brushing with a fluoridated dentifrice twice daily should be emphasized to help prevent caries and gingivitis. If a patient's sensory issues cause the taste or texture of fluoridated toothpaste to be intolerable, a fluoridated mouth rinse may be applied with the toothbrush. Toothbrushes can be modified to enable individuals with physical disabilities to brush their own teeth. Electric toothbrushes and floss holders may improve patient compliance. Caregivers should provide the appropriate oral care when the patient is unable to do so adequately.

A non-cariogenic diet should be discussed for long-term prevention of dental disease.[17] When a diet rich in carbohydrates is medically necessary, the dentist should provide strategies to manage the caries risk by altering frequency or increasing preventive measures. As well, other oral side effects (e.g. xerostomia and gingival over growth) of medications should be reviewed.

Sealants reduce the risk of caries in susceptible pits and fissures of primary and permanent teeth, and thus, patients with SHCN may benefit from sealants.[18] Topical fluorides may be indicated when caries risk is increased.[19] Interim therapeutic restoration,[20] using materials such as glass ionomers that release fluoride, may be useful as both preventive and therapeutic approaches in patients with SHCN.[18] In cases of gingivitis and periodontal disease, chlorhexidine mouth rinse may be useful. For patients who might swallow a rinse, a toothbrush can be used to apply the chlorhexidine. Patients having severe dental disease may need to be seen every 2–3 months or more often if indicated. Those patients with progressive periodontal disease should be referred to a periodontist for evaluation and treatment.

Restorative Care

Most children with SHCN are at high caries risk, and therefore, definitive treatment of primary teeth with preformed metal crowns (PMCs) is more favorable over time than intracoronal restorations. A review of the literature comparing PMCs and Class II amalgams concluded that, for multisurface restorations in primary teeth, PMCs are superior to amalgams.[21] The selection of more durable restoration is particularly important in patients receiving treatment under sedation or general anesthesia. PMCs are likely to last longer and possibly decrease the need for sedation or general anesthesia with its increased costs and its inherent risks.

Barriers

Dentists should be familiar with community-based resources for patients with SHCN and encourage such assistance when appropriate. While local hospitals, public health facilities, rehabilitation services, or groups that advocate for those with SHCN can be valuable contacts to help the dentist/patient address language and cultural barriers, other community-based resources may offer support with financial or transportation considerations that prevent access to care.[9]

Referral

If patient's needs are beyond the skills of the practitioner, he should make necessary referrals to ensure the overall health of the patient.[14]

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