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Original Article

A Study on Central Macular Thickness Changes in Diabetic Patients Undergoing Phacoemulsification

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Abstract

Aim: This study aims to assess central macular thickness (CMT) using optical coherence tomography (OCT) in diabetic patients before and after phacoemulsification.

Materials and Methods: A prospective study on 90 diabetic patients conducted from February 2018 to February 2019, who were all operated for cataract by phacoemulsification. Complete ophthalmological evaluation was done preoperatively. CMT was measured preoperatively using spectral-domain (SD) OCT. Patients were followed at the 1st post-operative day and at 1, 4, and 6 weeks postoperatively. OCT was done during the 6th week of post-operative period.

Results: The mean central 1 mm subfield macular thickness, preoperatively and 6th week postoperatively was 205.12 ± 24.85 μm and 212.79 ± 28.29 μm, respectively. The difference between pre-operative and 6th week post-operative CSMT was significant in all the three groups (no diabetic retinopathy (DR), mild non-proliferative DR [NPDR], and moderate NPDR) (*P* = 0.001).

Conclusion: SD-OCT detected statistically significant increase in mean CMT at 6-week postoperatively in diabetic patients undergoing phacoemulsification. Precise surgical technique, in the bag implantation of intraocular lens and good post-operative care, blood sugar control reduces the occurrence of macular edema, resulting in good visual outcome.

Key words: Phacoemulsification, Central Macular Thickness, Diabetes, Post cataract surgery

INTRODUCTION

Cataract is one of the common complications of diabetes mellitus, is a leading cause of blindness.[1] Majority of lens opacities in diabetics are nuclear sclerotic in type and they do progress more rapidly and become symptomatic at a younger age than in non-diabetics. Cataract surgery in diabetics is more problematic than non-diabetics. Macular edema (ME) is one of the most common causes of visual loss after uncomplicated cataract surgery. Diabetes has been associated with an increased incidence of post-operative ME.[2]

Cataract surgery-induced surgical trauma resulting in prostaglandins release and blood-retinal barriers disruption is thought to be the cause of ME.[3] Other causes could be vitreomacular traction and light-induced toxicity.

Phacoemulsification is most widely used cataract surgical technique nowadays. Various factors involved in phacoemulsification can influence the tissue structure of eyeball. The ultrasonic energy and fluidics produce mechanical effect that causes inflammatory reaction.

Optical coherence tomography (OCT) has been shown to be highly reproducible in measuring macular thickness in normal individuals and diabetic patients. It is an objective, non-contact, non-invasive, well-tolerated, and highly reproducible method for quantitative retinal thickness measurements, with good reproducibility and with approximately 10 μm resolution.[4] OCT is a well-established method of analyzing the *in vivo* retinal architecture. Spectral-domain (SD) OCT has replaced the conventional time domain OCT as it provides images of higher axial resolution and reduced motion artifacts.

The present study evaluates the changes in central macular thickness (CMT) preoperatively and postoperatively by SD-OCT in diabetic patients undergoing phacoemulsification.

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MATERIALS AND METHODS

This prospective study was designed to assess the effect of cataract surgery on central retinal thickness in diabetic patients. This study was conducted during the period from February 2018 to February 2019 at a tertiary eye care hospital. A total of 90 eyes were enrolled.

Inclusion Criteria

1. Patients aged >50 years with age-related cataract (senile) with diabetes undergoing cataract surgery (phacoemulsification), where fundoscopy and OCT evaluation of macular thickness are possible
2. No diabetic retinopathy (DR), mild and moderate non-PDR (NPDR) without diabetic maculopathy
3. Patients who are willing to come for regular follow-up.

Exclusion Criteria

1. Central corneal opacities
2. High myopic >5D or axial length more than 26.5 mm
3. Patients with present or past history of uveitis
4. Patients with dense cataract
5. Glaucoma patients
6. Patients with severe NPDR and PDR
7. Patients with diabetic maculopathy, clinically significant ME, and ME of any other pathology
8. Previous history of laser treatment
9. Presence of macular pathologies such as age-related macular degenerative changes involving macula, macular scars, choroidal neovascular membrane, and epiretinal membrane
10. Patients with intraoperative complications (posterior capsule rupture, dropped nucleus, vitreous loss, iris trauma, etc.).

Methodology

All patients selected for cataract surgery based on the above-mentioned criteria are evaluated by taking detailed history. Thorough ocular examination has been done, which include slit-lamp biomicroscopic examination, intraocular pressure by Goldmann applanation tonometer, fundoscopy using 90D, indirect ophthalmoscopy, A-scan biometry noting axial length of eye, and intraocular lens (IOL) power. Macular thickness assessment was done before and after cataract surgery using SD-OCT by a single person. Informed written consent was taken from all patients for inclusion in the study and for cataract surgery. Need for post-operative medical and regular follow-ups explained to each patient.

Study participants were grouped for comparison purposes by grades of DR, that is, no DR, mild NPDR, and moderate NPDR.

Patients were given antibiotic eye drops 1 day before operation day and advised to instill one drop hourly, during daytime. Pre-operative macular thickness measurement was done using SD-OCT. The three-dimensional macula protocol was used for macular thickness measurements.

Surgical technique was phacoemulsification with foldable IOL implantation by a single surgeon. Conventional phacoemulsification using Alcon Laureate machine done through a 3 mm temporal clear corneal incision. At the end of the surgery, a subconjunctival injection of 0.5 ml of gentamycin and 0.5 ml of dexamethasone was given in all cases. Postoperatively, all patients were prescribed a combination of dexamethasone and chloramphenicol eye drops in tapering doses for 8 weeks and cyclopentolate eye drops once a day for 1 week.

Post-operative slit-lamp findings were noted down. Visual acuity, anterior segment, and fundus examination findings recorded in all cases on the 1st post-operative day, 7th day, 28th day, and 6th week. OCT done at the 6th week of post-operative period.

Statistical Analysis

All data were analyzed by a descriptive analysis. Chi-square test was used for age, gender, eye laterality, grading of nuclear sclerosis, type of DR, duration of DR, and associated systemic diseases. ANOVA test was used for comparing effective phacoemulsification time and nuclear sclerosis grading. Paired sample *t*-test was used for measuring pre-operative and post-operative 6th week mean macular thickness in early treatment DR study subfields. General linear model was used for comparing type of DR and mean CSMT central 1mm subfield macular thickness.

$P < 0.05$ was considered to be statistically significant.

All the statistical calculations were done through SPSS for Windows (v16.0).

RESULTS

Demographics

Patients age ranged from 50 to 85 years in the study group. Mean age ± standard deviation (years) of patients was 64.14 ± 8.19 years. Males were 62 (65.9%) and females were 28 (31.1%) [Table 1 and Figure 1]. Majority of the patients were in the diabetic duration between 1 and 10 years (51.6%). Mean duration of diabetes in the study group was 8.71 ± 7.79 years. About 80% of patients had no DR, 15% had mild NPDR, and 5% had moderate NPDR.

Changes in Foveal Thickness (μm) in Post-operative Period

1. Preoperatively, the mean central 1 mm subfield macular thickness (CSMT) in the study group was

205.12 ± 24.85 μm. Postoperatively, the mean central 1 mm subfield macular thickness was 212.79 ± 28.29 μm [Table 2]. The difference was found to be statistically significant ($P = 0.001$)

2. The difference between pre-operative and 6th week post-operative CSMT was significant in all the three groups (No DR, mild NPDR, and moderate NPDR) ($P = 0.001$). The increase in mean CSMT, pre-operative, and 6th week postoperatively was higher in patients with moderate NPDR (26.5 μm) when compared to patients without DR (5.06 μm) and mild NPDR (13.44 μm) [Figure 2].

DISCUSSION

One of the important causes of reduced visual outcome after cataract surgery is ME. The incidence of ME has decreased due to the improvement in the cataract surgery from intracapsular cataract extraction to phacoemulsification combined with microincisional techniques and in the bag placement of IOL. Phacoemulsification is most widely used cataract surgical technique nowadays. Various factors involved in phacoemulsification can influence the tissue structure of eyeball. The ultrasonic energy and fluidics produce mechanical effect that causes inflammatory reaction.

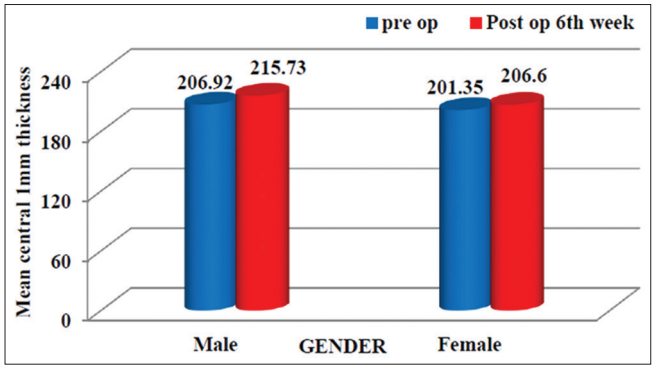

Figure 1: Mean central 1 mm macular subfield thickness in males and females in both groups

Diabetes has been associated with an increased incidence of post-operative ME.[3] The pathogenesis of edema is associated with destruction of blood aqueous retinal barrier by prostaglandins or other inflammatory mediators. Elevated levels of angiogenic factors, inflammatory cytokines, chemokines, and growth factors in aqueous play a role, which leads to increased post-operative inflammation which, in turn, leads to sight-threatening ME, aggravated by cataract surgery.[5]

The study was intended for analyzing the macular changes associated with phacoemulsification in diabetics using OCT. The clinical, demographic, pre-operative, and post-operative data in these patients were analyzed statistically.

In the present study, mean central 1 mm subfield macular thickness (CSMT) preoperatively and 6th week postoperatively was 205.12 ± 24.85 μm and 212.79 ± 28.29 μm, respectively, the difference being significant ($P = 0.001$) [Table 3].

Table 1: Demographics

Sex	Number
Male	62 (65.9%)
Female	28 (31.1%)
Total	90

Table 2: Mean central 1 mm subfield macular thickness between male and female in the study group

GROUPS	MEAN OF PRE OP CSMT (μm)	MEAN OF POST OP CSMT (μm)	*P* value
MALES	206.92 ± 25.32	215.73 ± 29.89	0.300
FEMALES	201.35 ± 24.03	206.60 ± 24.11	
TOTAL	205.12 ± 24.85	212.79 ± 28.29	0.001

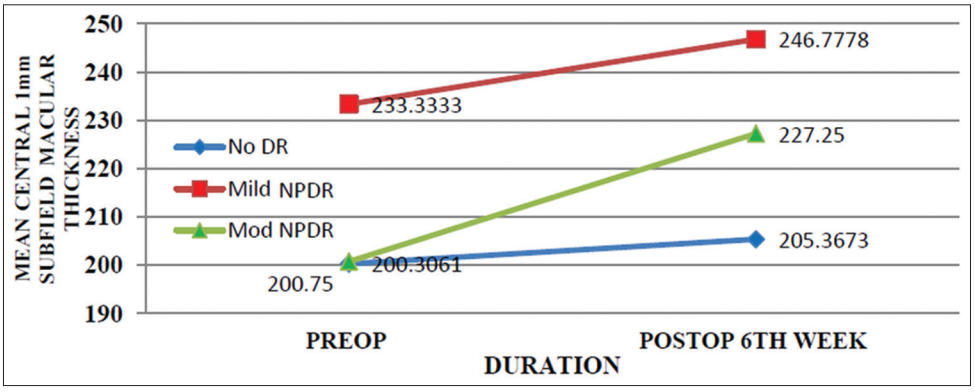

Figure 2: Comparison of pre-operative and post-operative mean central 1 mm subfield macular thickness (CSMT) in no diabetic retinopathy (DR), mild non-proliferative DR (NPDR), and moderate NPDR

Table 3: Comparison of pre-operative and post-operative mean central 1 mm subfield macular thickness (CSMT) in no diabetic retinopathy (DR), mild non0proliferative DR (NPDR), and moderate NPDR

DIABETIC STATUS	MEAN PREOP CSMT (μm)	MEAN POSTOP 6TH WEEK CSMT(μm)	*P* VALUE
NO DR	200.30 ± 19.96	205.36 ± 21.83	0.001
MILD NPDR	233.33 ± 31.77	246.77 ± 30.16	
MODERATE NPDR	200.75 ± 26.39	227.25 ± 39.68	
TOTAL	205.12 ± 24.85	212.79 ± 28.29	0.001

CSMT-- CENTRAL 1mm SUBFIELD MACULAR THICKNESS (CSMT)

In a study done by Katsimpris *et al.*,[6] pre-operative central foveal thickness was 205 ± 18 μm; and post-operative 1 month was 229 ± 21 μm. In a study done by Khedr,[7] CMT measured preoperatively was 201.84 ± 2.02 μm and post-operative CMT was 215.72 ± 3.4 μm.

In a study done by Pukl *et al.*,[8] pre-operative CMT was 238.6 ± 29.0 μm and 1 month postoperatively, CMT was 244.5 ± 24.0 μm.

In the present study, increase in mean CSMT, preoperatively, and 6th week postoperatively was higher in patients with moderate NPDR when compared to patients without DR and mild NPDR. This is similar to the study conducted by Sng *et al.*,[9] in which diabetic patients with moderate NPDR had greater mean CSMT than those with mild NPDR and no DR.

Kwon *et al.*[10] studied 104 subjects (36 men and 68 women). The number of patients without DR was 61 (58.65%), with mild-to-moderate NPDR was 27 (25.96%), and with severe NPDR or PDR was 16 (15.36%). The most common complication was ME, which were occurred in 19 eyes (18.27%) followed by retinopathy progression (11.54%). Among the 19 eyes with ME, 12 eyes (63%) developed ME at 1 month after surgery and 13 eyes (68%) showed improvement of ME by 6 months after surgery. The remaining 6 eyes did not improve by 6 months.

Although post-operative ME is more common in diabetics, it is found to resolve spontaneously in subjects with no or mild NPDR. Clinically significant ME tends to persist or may arise *de novo* or even worsen after cataract surgery in cases with moderate or severe NPDR. A thorough pre-operative evaluation of their retinopathy status is mandatory in these subjects. The need for cataract surgery, their retinopathy status, and the risk of progression should be well discussed with the subjects and their relatives.

We acknowledge some limitations to our study:

1. We did not have control group to compare with
2. Needs longer period of study to see if effects on retinal macular thickness were present or not.

CONCLUSION

- SD-OCT detected statistically significant increase in mean CMT at 6 weeks postoperatively in diabetic patients undergoing phacoemulsification
- The increase in mean macular thickness postoperatively did not affect final visual outcome
- Precise surgical technique, in the bag implantation of IOL and good post-operative care reduces the occurrence of ME, resulting in good visual outcome
- Control of diabetes and treatment of DR before cataract surgery minimizes post-operative retinal macular thickness.

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Original Article

A Study to Evaluate the Clinical Profiles of Asymmetric and Mixed Types of Intrauterine Growth Retardation

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Abstract

Introduction: The prevalence of intrauterine growth restriction (IUGR) is about 28% in the general population. IUGR poses increased risk of fetal mortality and morbidity and also contributes to developmental origin of health and disease. Of the three types of IUGR, Type III is more common in developing countries. This study evaluates the clinical profiles of Type II and Type III IUGR and also to evaluate any differences between the two types.

Materials and Methods: This cross-sectional, observational, and analytical study was conducted on 86 pregnant women with gestational age of more than 24 weeks, clinically diagnosed as IUGR and confirmed by ultrasound. They were followed up till discharge in the postnatal period. Any significant antenatal, intranatal, or postnatal events were recorded.

Results: There were increased incidences of oligohydramnios, preterm birth, and requirement of cesarean section which are increased in the cases of IUGR, more in Type II than in Type III IUGR. Furthermore, there were significant differences in maternal Vitamin D levels between the low and normal birth weight groups in Type II IUGR.

Conclusion: IUGR is associated with increased risk of preterm birth and operative delivery. Deficient maternal serum Vitamin D levels are a risk factor for low birth weight in asymmetric IUGR only, though further studies need to be conducted in this regard.

Key words: Asymmetric intrauterine growth restriction, Cesarean section, Mixed intrauterine growth restriction, Oligohydramnios, Preterm birth, Type II intrauterine growth restriction, Type III intrauterine growth restriction, Vitamin D

INTRODUCTION

Intrauterine growth restriction (IUGR) is defined as a velocity of fetal growth less than the normal fetus growth potential for a specific neonate as per the race and gender. Any fetus with sonographic estimated weight below the 10th percentile for gestational age (GA) is considered to have IUGR.[1]

The prevalence of IUGR is about 28% in the general population. The prevalence of IUGR is higher in Asia than elsewhere. It has been shown that 52% of stillbirths are associated with IUGR and 10% of perinatal mortality is a consequence of IUGR.[1] Apart from the increased risk of mortality, IUGR neonates also face many short-term and long-term complications, including fetal origin of adult disease, which has been recently replaced with "developmental origin of health and disease."[2]

Clinically, three categories of IUGR can be identified depending on the time of onset and the pathological process:[1]

1. Type I or symmetrical or intrinsic IUGR – this occurs as a result of growth inhibition early pregnancy. It accounts for 2030% of growth retardation. This type of IUGR leads to reduced number of cells in fetus and overall decreased growth potential caused by intrauterine infection, chromosomal disorders, and congenital malformation. All parameters, i.e. head and abdominal circumference, length, and weight are below 10th percentile for gestation age; hence, these infants have a normal ponderal index

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2. Type II or asymmetrical or extrinsic IUGR – this occurs as a result of restriction of nutrient supply *in utero*, i.e. uteroplacental insufficiency. It accounts 7080% of growth restriction. The onset occurs usually after 28 weeks of gestation. This type of IUGR has near-normal total number of cells, but the cell size is reduced. There is brain-sparing effect so that the head growth remains normal but abdominal growth slows down. The ponderal index is low with low birth weight (LBW) and abdominal circumference and fetal length leads to decrease amniotic fluid and chronic hypoxia and may result in fetal length
3. Type III or intermediate IUGR or mixed IUGR – it is a combination of Type I and Type II resulting in decreased number as well as decreased cell size accounts for 510% of all growth retarded.

Type I IUGR is due to early insult in multiplication of cells during fetal growth which is intrinsic pathological process genetically determined independent of any micronutrient deficiency while Type II and Type III IUGR are caused by extrinsic factors such as most of micronutrient deficiency result due to uteroplacental insufficiency results in poor differentiation of cells during fetal growth. Of the micronutrients, Vitamin D has been hypothesized as a cause for fetal growth restriction. The link between maternal Vitamin D status and fetal growth, as measured most frequently by infant birth weight and birth length, has been explored by a number of investigators with mixed result.[3] Thus, clearly, Type II and Type III IUGR may be preventable, to some extent, by addressing the modifiable factors.

Although there have been some comparative studies between symmetric (Type I) and asymmetric (Type II) IUGR, no studies were found involving mixed (Type III) IUGR. As Type III IUGR is usually seen in the developing countries[1] and also as Type II and Type III IUGR may be associated with preventable risk factors, therefore, this study was undertaken to understand the clinical profiles of Type II and Type III IUGR and also to evaluate any differences between the two types.

MATERIALS AND METHODS

This cross-sectional, observational, and analytical study was undertaken after approval of the Institutional Ethics Committee.

A total of 86 pregnant women attending antenatal clinic with gestation age more than 24 weeks and clinically diagnosed as IUGR were included in the study, after confirmation by the sonographic parameters. Pregnant women having any major comorbidities such as diabetes, parathyroid or bone disease, and anemia or any major high-risk condition associated with the current pregnancy such as antepartum hemorrhage, placenta previa, and pre-eclampsia were excluded from the study.

A written informed consent was obtained from each participant. Demographic details and routine obstetric history were recorded. Physical and obstetric examination was done. Routine investigations were carried out. Apart from that, the serum Vitamin D3 levels, serum calcium levels, and serum alkaline phosphatase levels were also recorded.

All the patients were followed up till discharge in the postnatal period. Any significant antenatal, intranatal, or postnatal events were recorded.

Statistical Analysis

The data were analyzed using SPSS. Qualitative data were analyzed using Chi-square test (Fisher's exact test when any cell value was <5) and quantitative data were analyzed by unpaired *t*-test. $P < 0.05$ was considered to be statistically significant.

RESULTS

Of the total 86 cases, the incidence of Type II IUGR was 84% (72 cases) and of Type III IUGR was 16% (14 cases). The overall prevalence of oligohydramnios, operative delivery by lower segment cesarean section (LSCS), and LBW is as per Table 1.

The prevalence of oligohydramnios was more in Type III IUGR group and the difference was statistically significant [Table 2].

No statistically significant differences were found in either the incidence of preterm deliveries ($P = 0.24$) or the birth weight ($P = 0.25$) in the two groups [Table 3].

The requirement of operative delivery (LSCS) was also significantly more in Type III IUGR group [Table 4].

On comparing the maternal serum levels of Vitamin D3, it was found that there was on overall deficiency [Table 5].

Table 1: Distribution of the characteristics in the study group

Parameter	Number of cases	Percentage
Oligohydramnios	39	45
Operative delivery (LSCS)	42	49
LBW (<2.5 kg)	55	64
Deficiency of Vitamin D3 (<50 nmol/L)	83	97
Deficiency of calcium (<8 mg/dL)	18	21
Neonatal death	1	1.2

LSCS: Lower segment cesarean section, LBW: Low birth weight

However, when grouped as per the type of IUGR, there was no statistically significant difference. However, when grouped as per the birth weight of the neonate, the group with LBW had a much lower maternal serum Vitamin D3 and that was statistically significant.

Table 2: Prevalence of oligohydramnios in Type II and Type III IUGR

Parameter	Type II IUGR (%)	Type III IUGR (%)	*P* value	Statistical significance
Oligohydramnios				
Present	25 (35)	14 (100)	<0.0001	Significant
Absent	47 (65)	0		

IUGR: Intrauterine growth restriction

Table 3: Comparison of incidence of preterm deliveries as per the type of IUGR

Parameter	Type II IUGR (%)	Type III IUGR (%)	*P* value	Statistical significance
Preterm delivery	20 (28)	3 (21)	0.24	Not significant
Term delivery	52 (72)	11 (79)		

IUGR: Intrauterine growth restriction

Table 4: Mode of delivery in Type II and Type III IUGR

Parameter	Type II IUGR (%)	Type III IUGR (%)	*P* value	Statistical significance
Delivery by LSCS	31 (43)	11 (79)	0.015	Significant
Normal/assisted	41 (57)	3 (21)		

IUGR: Intrauterine growth restriction, LSCS: Lower segment cesarean section

Maternal serum calcium levels were normal [Table 5] and no significant differences were found in terms of the type of IUGR or birth weight.

When maternal serum Vitamin D3 levels were compared in terms of birth weight in the Type II and Type III IUGR groups, no significant intergroup differences were found ($P > 0.05$). The only significant difference was found in the intragroup comparison in the Type II IUGR group [Table 6].

DISCUSSION

Fetal or IUGR is associated with perinatal mortality and morbidity. A satisfactory definition of IUGR has been suggested by the American College of Obstetricians and Gynecologists as describing "a fetus that fails to reach his potential growth."[2]

The recognition of IUGR begins with an accurate GA. Many studies have been conducted regarding the risk factors of IUGR. There have been some studies comparing the symmetric (Type I) and asymmetric (Type II) IUGR. However, no study was found regarding the studies profile of mixed IUGR. Therefore, this study was undertaken to compare the risk factors of asymmetric and mixed IUGR.

Oligohydramnios

The overall incidence of oligohydramnios is 15%.[4] However, in the study by Lin *et al.*,[5] the incidence of oligohydramnios was found to be significantly higher

Table 5: Intergroup comparisons of maternal serum levels of Vitamin D3 and calcium as per the type of IUGR and birth weight of the neonate

Parameter	Serum Vitamin D3 (in nmol/L)			Serum calcium (in mg/dL)		
	Mean±SD	*P* value	Significance	Mean±SD	*P* value	Significance
Type of IUGR						
Type II	27.52±10.23	0.189	Not significant	8.54±1.03	0.149	Not significant
Type III	24.96±9.57			8.82±0.88		
Birth weight						
Low	25.51±9.95	0.026	Significant	8.58±1.00	0.494	Not significant
Normal	29.92±9.96			8.59±1.03		

IUGR: Intrauterine growth restriction, SD: Standard deviation

Table 6: Intragroup comparison of maternal serum Vitamin D3 levels (in nmol/L) according to birth weight of the baby in the Type II and Type III IUGR groups

Type II IUGR				Type III IUGR			
LBW	Normal birth weight	*P* value	Statistical significance	LBW	Normal birth weight	*P* value	Statistical significance
Mean±SD	Mean±SD			Mean±SD	Mean±SD		
25.94±9.94	30.13±10.37	0.046	Significant	23.57±9.75	28.45±7.58	0.205	Not significant

LBW: Low birth weight, IUGR: Intrauterine growth restriction, SD: Standard deviation

in the IUGR group (29%) compared to non-IUGR group. Accordingly, in the present study, the incidence of oligohydramnios in IUGR was 45%.

All the cases of mixed IUGR were associated with oligohydramnios, in contrast to only 35% association in case of asymmetric IUGR.

Preterm Birth (Before 37 Weeks)

The overall preterm birth rate is 57% of the live births.[6] In the present study, the overall incidence was much higher (36.5%). Although IUGR has been hypothesized as a risk factor for preterm labor, the mechanisms of the relationship remain unknown. It has been hypothesized that IUGR increases susceptibility to preterm labor due to the changing balance of synthetic and metabolizing enzymes and hence increasing the availability of prostaglandins (key stimulants of labor).[7]

As per the study by Lin *et al.*,[8] the incidence of preterm labor was less in the cases of asymmetric IUGR as compared to symmetric IUGR.

In the present study, the incidence of preterm labor was slightly more with asymmetric IUGR than mixed IUGR. However, the difference was not statistically significant.

Cesarean Section

The overall cesarean section rate in India is 17.2%.[9] However, in the study by Boers *et al.*,[10] the cesarean section rate in the cases of IUGR was 44%. Accordingly, in the present study, the cesarean section rate was 49%.

In the study by Connor *et al.*,[11] the cesarean section rate was found to be significantly higher in the symmetric IUGR group (12%) than in the asymmetric IUGR group (5%).

In the present study, the rate was more in the case of mixed IUGR (79%) than in the case of asymmetric IUGR (43%).

Birth Weight

The incidence of LBW in India varies between 25% and 30% and of which 60% and 65% are due to IUGR.[12] In accordance, the incidence of LBW in the present study was found to be 64%.

As per the studies by Lin *et al.*[8] and Connor *et al.*,[11] it was concluded that the birth weight was more in cases of asymmetric IUGR than in symmetric IUGR.

In the present study, no statistically significant difference was found in the incidence of LBW between the asymmetric and mixed IUGR groups.

Vitamin D3

In the present study, the prevalence of deficiency of Vitamin D3 in IUGR cases was 97%. This is in accordance to the high prevalence of Vitamin D deficiency in cases of IUGR in the studies by Nageshu *et al.* (68%),[13] Aly *et al.* (66%),[14] Hollis *et al.* (84%),[15] and in the systematic review by Aghajafari *et al.*[16]

It was also found in this study that the birth weight of the neonate was associated with maternal serum Vitamin D3 levels. The mean maternal serum Vitamin D3 level was significantly lower in the group with LBW babies than with normal birth weight babies. This was in accordance with the study by Nageshu *et al.*[13] and with the systematic review by Aghajafari *et al.*[16] However, these were in contrast to the study by Gale *et al.*[17]

When analyzed according to the type of IUGR, statistically significant difference was found between maternal serum Vitamin D3 levels in low and normal birth weight groups in the asymmetric IUGR group. However, this difference was not significant in the mixed IUGR Group. Thus, maternal serum Vitamin D3 levels have a significant impact on the birth weight of the neonate in the case of asymmetric IUGR.

Limitations

The study was limited by the outpatient department attendance of the pregnant women with IUGR. Therefore, the results may not be generalized.

CONCLUSION

It can be effectively concluded from the study that the incidences of oligohydramnios, preterm birth, and requirement of cesarean section are increased in the cases of IUGR. Furthermore, these incidences are significantly different in the asymmetric (Type II) and mixed (Type III) IUGR cases. Low levels of maternal serum Vitamin D3 lead to LBW, particularly in cases of asymmetric IUGR. Thus, the deficiency of maternal serum Vitamin D3 as a risk factor for LBW in IUGR is supported only in case of asymmetric IUGR but not in mixed IUGR, though further studies need to be conducted in this regard.

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Original Article

Effects of Nebulized Dexamethasone Versus Nebulized Ketamine on the Attenuation of Post-operative Sore Throat Following Endotracheal Intubation

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Abstract

Background: General anesthesia (GA) with endotracheal intubation is a frequent cause of airway mucosal trauma which results in the post-operative sore throat (POST), with an incidence of 21–65%. Although minor and self-limiting complication, it produces significant discomfort and annoyance to the patient. This study was aimed to compare the efficacy of nebulized dexamethasone versus ketamine in preventing POST.

Materials and Methods: After approval from the institutional ethics committee and written informed consent, 100 patients of the American Society of Anesthesiologists physical status 1–2, aged between 20 and 60 years of either sex, undergoing GA with endotracheal intubation were included in this prospective, randomized, and double-blind study. Patients were randomized into two groups of 50 each (n = 50); Group D: Patients received dexamethasone 8 mg (2 ml) with 3 ml of normal saline (total volume of 5 ml) for nebulization and Group K: Patients received ketamine (preservative free) 50 mg (1 ml) with 4 ml of normal saline (total volume of 5 ml) for nebulization. After 15 min of nebulization, induction was done, POST assessment was done at 0, 2, 4, 6, 12, and 24 h post-extubation. The severity of POST was graded on a 4-point scale (0–3).

Results: The total incidence of POST was 19% in this study. Five patients (10%) in dexamethasone group and 14 patients (28%) in ketamine group experienced POST (Fisher's exact test, P = 0.039). Reduction in the incidence and severity of POST in the dexamethasone group when compared to ketamine group at 2, 4, 6, and 12 h postoperatively is statistically significant (P < 0.05*).

Conclusion: Pre-operative single dose of nebulized dexamethasone 8 mg effectively attenuates POST in patients following GA with endotracheal intubation compared to nebulized ketamine 50 mg without any detrimental effects.

Key words: Dexamethasone, General anesthesia, Intubation, Ketamine, Nebulization, Sore throat

INTRODUCTION

Post-operative sore throat (POST) is a frequent complaint that occurs in 21–65% of patients receiving general anesthesia (GA) with endotracheal intubation.[1,2] Even though considered as a minor and self-limiting complication, it may cause discomfort, distress to the patients and may even lead to significant post-operative morbidity.[3]

Many treatment modalities both non-pharmacological and pharmacological have been tried for attenuating POST with varying results.[4] Some of them include the use of small size endotracheal tubes, low intracuff pressures,[5,6] minimizing laryngoscopy attempts, use of topical lidocaine,[7] spraying the endotracheal tube with beclomethasone,[8] gargling with ketamine and magnesium sulfate ($MgSO_4$),[9,10] nebulization with ketamine and $MgSO_4$,[11-13] $MgSO_4$ lozenges,[14] and inhalational steroids.[15]

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Corticosteroids have anti-inflammatory action and are widely used in clinical practice. The inhaled steroids distribute the drug to the airways and are devoid of systemic effects. Dexamethasone is a potent, long-acting synthetic steroid with anti-inflammatory effects, superior to other steroids. Various studies have been reported, supporting its use in effectively relieving POST.[16]

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist with anti-nociceptive and anti-inflammatory effects and has been used successfully in the form of gargle for reducing POST. In view of a few disadvantages associated with ketamine gargle and lozenges such as the bitter taste, need for larger volumes, and risk of accidental aspiration, ketamine was used by the aerosol route to overcome these problems and for better patient tolerance.

The aim of this study was to assess and compare the effectiveness of nebulized dexamethasone versus ketamine in preventing the incidence and severity of POST following endotracheal intubation in patients under GA and also to detect any adverse effects.

MATERIALS AND METHODS

This prospective, randomized, and double-blind study was conducted in a tertiary care Government General and Teaching Hospital from March 2019 to September 2019. After obtaining the Institutional Ethical Committee approval and written, informed consent, 100 adult patients of ASA physical status I and II, aged between 20 and 60 years of either sex, undergoing elective surgeries under GA with endotracheal intubation, lasting <2 h duration were enrolled in this study. Exclusion criteria were patients with a history of pre-operative upper respiratory tract infection, asthma, sore throat, allergy to study drug, recent use of nonsteroidal anti-inflammatory drugs, anticipated difficult airway with Mallampati Grade >2, pregnancy, diabetes, undergoing head-and-neck surgeries, oral, nasal, and surgeries in the prone position.

The sample size was calculated based on the findings of the pilot study which was conducted with a sample of 20 patients, 10 per each group. To show 50% reduction in the incidence at α-error of 0.05 and power of 90%, we required sample size of 48 patients per group. Hence, 50 patients were included in each group to account for dropouts. The patients taken for the pilot study were not included in the original study.

Patients were randomized into two groups of 50 each using the randomization technique by an anesthesiologist who was not involved in the study. The nebulization solution was prepared according to group allocation by anesthesia assistant who did not participate in further assessment of these patients. As both the nebulization solutions were colorless and tasteless, patients were blinded to the study drug preparations.

All the patients were kept nil oral overnight preceding surgery. On arrival at the operation theater, after securing IV cannula, all the standard monitors such as non-invasive blood pressure, electrocardiogram, pulse oximetry (SpO_2), and capnography were attached and baseline parameters were recorded. GA was administered as per the standard protocol for all the patients. Before the start of GA, 15 min before induction, all the enrolled patients received the study drugs by nebulization mask attached to wall-mounted oxygen source at 8 L/min, for 15 min according to group allocation.

Group D: Patients received dexamethasone 8 mg (2 ml) with 3 ml of normal saline (total volume of 5 ml) for nebulization.

Group K: Patients received ketamine (preservative-free) 50 mg (1 ml) with 4 ml of normal saline (total volume of 5 ml) for nebulization.

After 15 min of nebulization, patients were premedicated with intravenous (IV) injection glycopyrrolate 0.2 mg, injection fentanyl 2 mcg/kg, and midazolam 0.02 mg/kg. After preoxygenation with 100% oxygen for 3 min, induction was done with injection thiopentone IV 5 mg/kg. Tracheal intubation was done by smooth and gentle laryngoscopy 3 min after administering injection vecuronium bromide 0.1 mg/kg by an experienced anesthesiologist. Single-use, sterile, high-volume low-pressure cuffed polyvinyl chloride endotracheal tube with an internal diameter of 7–7.5 mm for females and 8–8.5 mm for males was used. The tracheal cuff was inflated with a volume of room air until no audible air leak and cuff pressure were set to 20 cm H_2O using hand gripped cuff pressure monitor and monitored every 30 min to maintain cuff pressure of 20 cm H_2O till the end of surgery. GA was maintained in both the groups with oxygen 33% in nitrous oxide 67%, sevoflurane 1–2%, and intermittent doses of IV vecuronium and fentanyl. Half an hour before the completion of surgery, injection IV ondansetron 4 mg was administered to prevent post-operative nausea and vomiting and then 8th hourly thereafter. At the end of the surgery, oropharynx was gently suctioned, and the neuromuscular block was reversed using injection IV neostigmine 0.05 mg/kg and injection glycopyrrolate 0.001 mg/kg. Tracheal extubation was performed in a

similar way in both the groups after complete recovery and the patient was fully awake.

After extubation, the patients were shifted to the post-anesthesia care unit for observation and assessment. Injection paracetamol 1 g IV was given 8th hourly. Patients were assessed for incidence and severity of POST at 0, 2 4, 6, 12, and 24 h postoperatively, starting from the time of extubation by an anesthesia resident who was blinded to the study.

The incidence of POST was assessed by asking the patient for the presence or absence of soreness, pain, and change of voice or any discomfort in the throat. The severity of POST was graded on a 4-point scale (0–3)[9] assessed as per the following clinical scores:

0–3 points scale

Grade 0 = no sore throat.

Grade 1 = mild sore throat (complains of sore throat only on asking).

Grade 2 = moderate sore throat (complains of sore throat on his/her own).

Grade 3 = severe sore throat (change of voice or hoarseness, associated with throat pain).

Any side effects such as cough, dry mouth, post-operative nausea vomiting, and respiratory depression were noted 8th hourly during the first 24 h postoperatively.

Statistical Analysis

All the collected data were entered into Microsoft Excel and statistical analysis was done using GraphPad.com software and Vassarstats.net software. Data were expressed as mean, standard deviation, and/or ratio or absolute numbers (%) and compared using Student's *t*-test, Fisher's exact test, and Chi-square test whichever were applicable. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 103 patients were screened for this study. Out of these, three patients were excluded due to various reasons such as one patient had a history of asthma, one patient was morbidly obese with Mallampati Grade >2, and one patient with ASA physical status >2. Hence, a sum of 100 consented patients who fulfilled the inclusion criteria and randomized into two groups of 50 each was included in the study for their post-operative assessment of sore throat (POST) and completed the study successfully.

Demographic data were comparable between the two groups. There was no statistically significant difference between the two groups in terms of age, sex, body weight, ASA physical status, and duration of surgery [Table 1].

The comprehensive incidence of POST was 19% in the present study. Five patients (10%) in Group D and 14 patients (28%) in Group K contacted POST at 1 point of the study (Fisher's exact test, $P = 0.039$).

In the immediate post-operative period at 0 h, there was no significant difference in the incidence of POST in between the two groups ($P = 0.066$). Incidence of POST was significantly lower in Group D at 2, 4, 6 and 12 h post-extubation when compared to Group K. At 2 h and 4 h post-extubation, 5 patients in Group D developed POST compared to 14 patients in Group K ($P = 0.039$) which was statistically significant. At 6 h postoperatively,

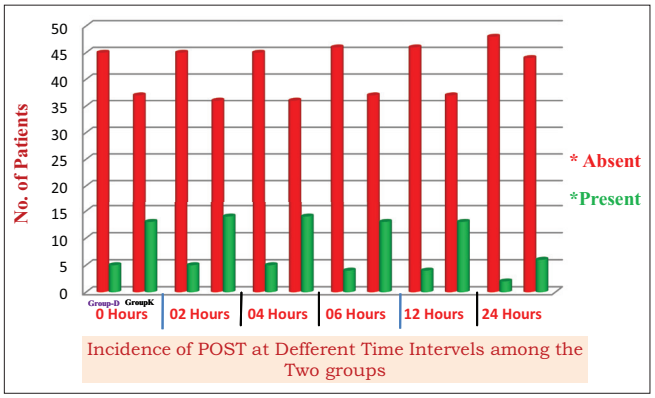

Figure 1: Incidence of post-operative sore throat at different time intervals among the two groups

Table 1: Demographic data of the patients

Parameters	Mean±SD (*n*=50)		*P*
	Group D	Group K	
Age in years	39.42±10.31	41.30±9.56	0.150
Weight in kg	64.57±8.45	66.29±7.82	0.322
Gender (male/female) (*n*)	29/21	26/24	0.687*
ASA I/II	31/19	33/17	0.835
Duration of surgery (min)	88.29±18.62	91.81±15.6	0.308

Data expressed as mean (SD) or ratio or absolute numbers, Student's *t*-test, *Fischer's exact test, SD: Standard deviation

Table 2: Incidence of post-operative sore throat in patients

Time period (hour)	Sore throat incidence	Group D *n*=50	Group K *n*=50	*P*
0	Absent	45	37	*P*=0.066
	Present	5	13	
2	Absent	45	36	*P*=0.039
	Present	5	14	
4	Absent	45	36	*P*=0.039
	Present	5	14	
6	Absent	46	37	*P*=0.010
	Present	4	13	
12	Absent	46	37	*P*=0.010
	Present	4	13	
24	Absent	48	44	*P*=0.268
	Present	2	6	

Values are expressed as absolute numbers. Fischer's exact test used, *P*< 0.05 statistically significant.

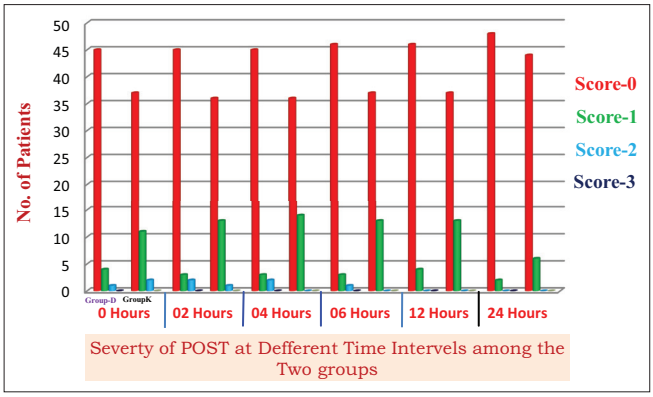

Figure 2: Severity of post-operative sore throat at different time intervals among the two groups

Table 3: Severity of post-operative sore throat in patients

Time period (hour)	Sore throat grade					*P*
		0	1	2	3	
0	Group D	45	4	1	0	*P*=0.223
	Group K	37	11	2	0	
2	Group D	45	3	2	0	*P*=0.040
	Group K	36	13	1	0	
04	Group D	45	4	1	0	*P*=0.020
	Group K	36	14	0	0	
06	Group D	46	3	1	0	*P*=0.025
	Group K	37	13	0	0	
12	Group D	46	4	0	0	*P*=0.031
	Group K	37	13	0	0	
24	Group D	48	2	0	0	*P*=0.135
	Group K	44	6	0	0	

Values are expressed as absolute numbers. *Chi-square test used, *P*< 0.05 statistically significant.

POST was observed in 4 patients in Group D compared to 13 patients in Group K ($P = 0.010$) which was statistically significant and identical statistically significant results were observed at12 h postoperatively ($P = 0.010$). There was no significant difference at 24 h post-extubation in between the groups ($P = 0.268$) [Table 2 and Figure 1].

When comparing for the severity of POST in between the two groups using a 4-point scale, POST was significantly abated in Group D at 2 h ($P = 0.04$), 4 h ($P = 0.012$), 6 h ($P = 0.041$), and 12 h ($P = 0.044$) postoperatively when compared to Group K. There was no significant difference in the severity of POST at 24 h post-extubation ($P = 0.537$). None of the patients experienced severe sore throat (POST Score 3) in both the groups [Table 3 and Figure 2]. No adverse effects were observed throughout the study.

DISCUSSION

GA with endotracheal intubation is associated with a number of major and minor complications, of which POST is one of the most commonly encountered minor complications.

Various causes have been attributed to the occurrence of POST such as trauma to the mucosa during laryngoscopy, repeated attempts at intubation, mechanical irritation of the airway with inflammation, and high intracuff pressures.[17] Different pharmacological trials and non-pharmacological techniques have been tried previously for the prevention of POST. Although various drugs were used through different routes to alleviate POST in earlier studies, some are associated with unwanted side effects and need for acceptance and cooperation from the patient. We chose the inhalational route for administering drugs in our study due to its ease of administration, low cost, rapid action, safety, convenience, need of a minimal dose of the drug, and topical effects avoiding systemic adverse effects.

The present study was undertaken to evaluate and compare the effectiveness of nebulized dexamethasone versus ketamine in alleviating POST following GA with endotracheal intubation.

The past literature supports the use of topical, intravenous, and inhaled steroids such as betamethasone gel and IV dexamethasone for the treatment of POST.[18] Due to the concerns associated with the use of IV steroids, we used nebulized dexamethasone as the route of choice in our study.

The total incidence of POST in our study was 19%, of which 5 persons (10%) in Group D and 14 persons (28%) in Group K developed POST.

Tabari *et al.*,[19] in their study, compared the effects of the application of betamethasone gel to the endotracheal tube cuff with intravenous dexamethasone and concluded that the topical application of betamethasone gel effectively reduced POST. These findings are in accordance with our study, wherein we used nebulized dexamethasone for its topical effects on the upper airway.

Lee *et al.*[20] found that the incidence of POST was reduced to 27% in their study on the effects of topical dexamethasone on a POST, whereas in our study, nebulized dexamethasone resulted in a much lower incidence of 10% due to its topical effects.

Ashwini *et al.*[21] have reported an incidence of 27.5% of POST in the dexamethasone group in their study on nebulized dexamethasone versus $MgSO_4$ in the prevention of POST. When compared to their study, our study showed an incidence of 10% in the dexamethasone group which was much lower.

Atef K. Salama *et al.*[22] demonstrated that a single dose of 8 mg of nebulized dexamethasone reduced the incidence and severity of POST at 0, 2, 4, 6, and 12 h post-extubation of post-operative assessment. These observations are similar to the findings of our study, except for the immediate post-operative period.

Zhu *et al.*[23] demonstrated in their experimental study on animals that, ketamine an NMDA receptor antagonist, by its topical effect, attenuated the local inflammation induced by trauma and showed a protective effect on airway through nebulization route. In our study also, we preferred ketamine by inhalational route for a similar reason.

Chan *et al.*[24] evaluated the topical action of ketamine gargle in reducing the incidence and severity of POST by observing low intraoperative serum levels of ketamine. The observations of Chan *et al.* study correlated with our study, except that we used nebulized ketamine for abating POST by its topical effects.

Shaaban *et al.*[25] in their comparative study between betamethasone gel applied over endotracheal tube and ketamine gargle for attenuating POST, proved that both were effective in reducing POST but betamethasone use being superior. These effects are in agreement with our study, wherein nebulized steroids proved superior to nebulized ketamine in preventing POST.

We fulfilled all the inclusion and exclusion criteria and tracheal intubation was performed by an experienced anesthesiologist.

There are few limitations of our study. First, we were unable to measure serum concentrations of the study drugs, dexamethasone and ketamine to monitor drug levels during the study period due to lack of feasibility in our institute. The concern with ketamine is its effect on the recovery profile of the patients at the end of the surgery. In this study, the dose of nebulized ketamine administered is a single dose of 50 mg and its overall effect on the recovery of patients was negligible. At the end of the surgery, all the patients in both the groups had good recovery according to the modified Aldrete's recovery score. Second, the scale used to assess the POST score was a subjective scale and may be associated with bias.

CONCLUSION

We conclude from our study that the pre-operative single dose of nebulized dexamethasone 8 mg effectively attenuates the incidence and severity of POST following GA with endotracheal intubation than nebulized ketamine 50 mg with no adverse effects.

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Original Article

Hepatic Dysfunction in Children Suffering from Dengue Fever

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Abstract

Background: Dengue infections are associated with liver involvement leading to the occasional occurrence of liver failure of severe variety and even death. Dengue is almost endemic throughout India and it is much more serious and deleterious in children. We have, therefore, tried to estimate the prevalence of derangement of liver function in children affected with dengue virus infection.

Materials and Methods: This study was done in admitted dengue patients in our medical college in the age group of 1 month–12 years. Only 81 children of NS1 positive for dengue virus were included in the study. In all of these complete blood count and liver function tests were performed on the day of admission and every alternate date as long as they were admitted.

Results: All the parameters that are serum glutamic-oxaloacetic transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT), and gamma glutamyl transferase (GGT) raised throughout the whole period of dengue illness and the serum albumin level were reduced. However, these changes were most marked on the 5th–6th days of fever after which they again slowly waned.

Conclusion: Dengue fever causes hepatic injury in children, which is reflected by raised SGOT, SGPT, and GGT and reduced serum albumin. More the severity of the dengue infection more pronounced are the changes in liver derangement.

Key words: Dengue in children, Hepatic dysfunction, Severe dengue

INTRODUCTION

Dengue is an infectious febrile disorder caused by an arbor virus belonging to the genera of single standard enveloped RNA viruses. Dengue virus has four serotypes (DENV 1–4) and is a member of Flaviviridae family and the genus *Flavivirus*.[1] In recent years, dengue fever has come as an important epidemic in many parts of the world and has been a menacing name in India also. It has now probably superseded the number of incidences of malaria and is at present, bearing a huge number of sufferers throughout the world, the annual incidences of dengue being more than a million in a year spreading over 125 countries.[2]

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Regarding the complications of dengue, we generally mean dengue hemorrhagic fever and dengue shock syndrome. However, the occurrence of hepatic involvement in dengue is neither or less significant nor of any rare occurrence. In fact, involvement of liver complications in dengue is quite frequent and of quite serious consequences also, often leading to acute hepatic failure and even coma or death.[3,4] This is more of significance in children affected by dengue.

The common sequelae of hepatic failure from any cause (e.g., hepatitis A, B, or C) are: Acute liver failure leading to shock, coma, or even death; more chronic causes such as cirrhosis of liver, portal hypertension, hepatic encephalopathy, hepatorenal syndrome, and even cardiac failure. These all can occur following hepatic involvement as a consequence of dengue. Therefore, mortality due to hepatic involvement of dengue is quite high.

Shock is generally considered as the cause of liver failure in dengue but the same can occur even without any occurrence of shock.[5] Therefore, it is important to

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understand and assess the exact causes of liver failure in dengue. This is all the more important in case of children as they are the more vulnerable population and also for other obvious reasons. Apart from shock the other causes attributed in liver failure are direct attack of dengue viruses on hepatocytes, hypoxic damages of liver cells, and also immune-mediated apoptosis.[6] With all these facts in hand, we have tried to estimate the morbidity features of hepatic involvement of dengue fever in children.

MATERIALS AND METHODS

Study Place

The study was conducted on admitted pediatric dengue patients in a medical college hospital in the mid part of Bengal. In all of them complete blood counts (CBC), liver function tests (LFT), and other test for dengue (IgM and IgG) were performed. CBC and LFT were repeated on every alternate dates as long as they were admitted.

Period of Study

The study was conducted over a period of 1 year 3 months, i.e., March, 2018–June 2019

Inclusion Criteria

The following criteria were included in the study:

1. Serologically confirmed (NS1 ELISA and/or IgM MAC ELISA positive) dengue fever patient admitted to the department of pediatrics of our medical college
2. All cases in the pediatric age group (>1 month–12 years) were included irrespective of gender
3. Informed consent from parents and guardians were taken before undergoing the study.

Exclusion Criteria

The following criteria were excluded from the study:

1. Children with pre-existing liver diseases
2. Those patients (parents/guardians) who refused to take part in the study.

Sample size

In total, 81 patients were included in the study.

Study parameters/variables

I. Age
II. Gender
III. Urban/Rural
IV. Dengue serological test (NS1 ELISA and/or IgM MAC ELISA done in the department of microbiology
V. Complete hemogram including platelet count (done in the department of pathology)
VI. Liver function test (By LFT we mean serum bilirubin and its fractions, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], total protein, albumin, and globulin).

Study design

This study was conducted at institute based cross-sectional study.

Study tools

1) Preformed history sheet to record the above-mentioned parameters
2) Laboratory test results
3) Bed-head-ticket of the patient.

Study technique

NS-1 Ag and/or MAC ELISA for anti-dengue IgM specific antibodies in all fever cases in the said age group admitted in the pediatric medicine ward of our medical college and hospital during the specified study period for MAC ELISA history of fever should be 5 days or more and features suggestive of dengue.

Cases diagnosed as dengue positive when — detection of IgM antibody in single serum sample and/or NS-1 antigen positive for dengue virus.

Among the patients identified by the above technique as dengue positive cases, only those meeting the inclusion criteria of the study and consenting to take part in the study were included in the final study.

Analysis of Data

Data were collected, recorded, and compiled on Microsoft Excel 2007 datasheet. After the end of the study, all the data were compiled, tabulated, and statistically analyzed, and inferences drawn.

RESULTS

Out of total 81 dengue patients, 8 (9.88%) patients were diagnosed as severe dengue. Age-wise distribution of

Table 1: Age-wise distribution of dengue cases

Age in years	PD	D+WS	SD	Total
<1	-	1	1	2
1–2	2	4	-	6
2–3	3	2	1	6
3–4	4	3	1	8
4–5	6	6	1	13
5–6	2	3	1	6
6–7	3	5	1	9
7–8	3	3	2	8
8–9	3	4	-	7
9–10	1	3	-	4
10–11	9	1	-	10
11–12	1	1	-	2
Total	37	36	8	81

PD: Probable dengue, D+WS: Dengue with warning signs, SD: Severe dengue

patients of dengue is depicted in Table 1. Amongst these, 53 patients were male children and rest patients 28 were female. Thirty-three patients were rural and forty-eight were urban. Derangement of liver function is depicted in Table 2.

DISCUSSION

In the present study, we measured the liver enzymes serum glutamate-pyruvate transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT), GGT, and ALP from day 1 then every alternate day till the day of discharge. It was found that excluding ALP which was raised only occasionally all the other three enzymes were raised throughout the whole period of dengue fever. The peak of the rise on an average was on day 5 of illness.

Fernando *et al.* from Sri Lanka found that all the patients with severe dengue had some degree of liver involvement while almost 85% of all patient with non-severe dengue had also some raised hepatic enzymes.[6] It is already established that raised levels of SGPT and SGOT are deemed as sine qua non of hepatic cell injury as these enzymes profusely poured into general circulation following a liver cell injury.

Out of these two SGPT though also present in skeletal muscle, brain, and intestine but in very low concentration and its rise is considered to be highly specific for liver cell injury only, on the other hand, rise of SGOT is seen not only in liver disorder but also in cardiac muscles, skeletal muscle injuries and is only a good supportive indicator of hepatic injury.[7] In their study, the elevation of SGOT was more pronounced than that of SGPT in severe damage suggesting that in severe dengue patient there is not only damage to liver cells but also concomitant injury to cardiac and or skeletal muscle. Our study also suggests that, since we did not perform the estimation of other most specific cardiac biomarkers; creatine phosphokinase-MB and cardiac troponin T and I and neither did we do skeletal muscle-specific enzymes; creatine kinase and serum aldose, we cannot conclude with surety that concomitant damage of cardiac and skeletal muscle occur also in severe dengue.

However, the presence of severe myalgia in dengue suggests all associated skeletal muscle damage but lack of any cardiac symptoms apparently rules out possible cardiac muscle damage in severe dengue. However, a more detail cardiac studies should be done to rule out any possibility of cardiac involvement particularly in severe dengue cases. Some of patients particularly severe dengue had rise in serum bilirubin with pronounced rise in conjugated bilirubin suggesting a frank hepatocellular jaundice. Serum albumin also is reduced in only a few cases of severe dengue suggesting that the synthetic function of liver is the last item among the various liver function to be disrupted in dengue fever. Clinically, hyperbilirubinemia (more than two milligram per deciliter) with frank jaundice is also seldom seen in dengue fever except severe dengue where it is fairly common.

In our study, we had a mild rise in GGT and practically no rise in ALP. Both of these are signs of cholestasis in liver disorder but rise in ALP is a much better marker and most specific for cholestasis whereas it is not that specific. The latter is also raised in acute oxidative stress. Hence, the non rise of ALP and mild rise of GGT suggest that there is not much cholestasis in dengue liver derangement but there is definitely some acute oxidative stress. Acute oxidative stress causes reduction in cellular glutathione level with subsequent rise in GGT.[8,9] Hence, a rise of GGT in our study could be attributed to an acute oxidative stress. However, we should have measured serum 8 hydroxydeoxyguanosine levels to understand the levels of DNA damage to hepatocytes and other cells due to oxidative stress in dengue.

Narasimhan *et al.* also found hepatic involvement in dengue fever and noted that spectrum of liver disorder in dengue ranges from mild and asymptomatic biochemical derangement to severe jaundice and even total hepatic failure.[10] Low albumin levels are marker of clinical phase of the disease. Larreal *et al.* reported jaundice in two out of 63 cases of dengue fever.[11] Soni *et al.* also found liver disorder in dengue and like in our study they also noted higher SGOT than SGPT.[12] In a study from Pakistan found more than 3% of patients of dengue had hyperbilirubinemia comparable to our study which shows about 5% of such cases.[13]

Table 2: Derangement of liver function in dengue patients

Parameters	Day 1 on admission	Day 3 on admission	Day 5 on admission	Day 7 on admission	Day 9 on admission
Bilirubin mg/dl	1.8	2.1	2.66	2.31	1.84
SGOT IU/L	81	192	287	192	114
SGPT IU/L	69	177	254	157	98
GGT IU/L	58	96	126	102	82
Alk phosphatase IU/L	76	114	138	105	71
Albumin g/dl	4.2	4.1	4.3	4.2	4.1
Globulin g/dl	2.2	2.3	2.1	2.3	2.1
Platelet count Lacs/dl	0.86	0.79	0.76	0.84	1.1

SGPT: Serum glutamate-pyruvate transaminase, SGOT: Serum glutamic-oxaloacetic transaminase, GGT: Gamma-glutamyl transferase

Limitations of our study:

1. Done only in admitted children with dengue who are naturally more serious than those treated for dengue at home
2. Prothrombin time was not estimated in these dengue patients
3. Degree of oxidative stress was not measured.

Strength of power study:

Done in children infected with dengue whereas, very few studies have been done on children.

CONCLUSION

In short, it can be concluded that within the limits of our study background in admitted children there is definitely damage of the liver in almost all cases of dengue. More the severity of dengue more is the height of hepatic damage.

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Original Article

A Study on the Clinicopathological, Molecular (Beta-hCG), Sonological Study, and Correlation in Breast Diseases

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Abstract

Introduction: Breast is important organ of female as a symbol of womanhood and fertility. This study is done to know utility of ultrasonography in identifying breast diseases as mammography not routinely available in all treating centres. Role of BetahCG in breast diseases.

Materials and Methods: This is a prospective observational study consisting of 112 patients with breast diseases planned for surgical management from June 2016 to June 2018 and a cyto-sono-histopathological correlation done. Pre-operative evaluation included history, clinical examination, ultrasonography (USG) breast, serum beta-human chorionic gonadotropin (hCG), and post-operative histopathology.

Results: The most common benign lesion was fibroadenoma (62 cases) followed by gynecomastia disease – 5 cases (7.33%). The most common malignant lesion reported in the study was invasive ductal carcinoma – 53 cases. In this study, sensitivity and specificity of breast fine-needle aspiration cytology (FNAC) were 87.5% and 100%, respectively. The diagnostic accuracy of FNAC in our study was reported to be 96.5%. Sensitivity and specificity of breast USG were 84.8.5% and 96.5%, respectively. The diagnostic accuracy of USG in our study was reported to be 93.3%. In our study, a 98.9% cyto-histopathological correlation was observed for benign lesions and 100% for cases suspicious of malignancy. A cyto-histopathological correlation was 100%.

Conclusion: Study concludes that sonography should be the first investigation to be done after the clinical examination because if USG says the disease is benign then the patient can be assured without any invasive procedure, i.e., FNAC and biopsy. If USG says abnormality then the patient should go for an invasive procedure. As far as for early definitive diagnosis, FNAC is superior to Sonology. Serum beta-hCG has no correlation with breast diseases.

Key words: Breast diseases, Fine-needle aspiration cytology, Histopathology, Serum beta-human chorionic gonadotropin, Sonology

INTRODUCTION

The breast has been a symbol of womanhood and ultimate fertility. Being superficially placed in the body has prompted interest of surgeons since the earliest period in the history of medicine. Cosmetic consideration and feel of mutilation have hampered in the early diagnosis of carcinoma breast. Breast is found in both sexes but it is rudimentary in males and for females, the mammary gland is a unique organ which is not fully formed at birth, undergoes cyclical changes during reproductive life. It develops into an important accessory organ of the female reproductive system and child nursing. A few breast diseases occur during reproductive life while some occur during the menopausal period indicating the relation of these diseases to hormonal stimulation as a causative factor.[1]

Breast is a modified sweat gland, comprising of glandular, fibrous, and fatty tissue. It became spot for various lesions

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ranging from mastitis to invasive carcinoma, over a wide range of age. Differentiation of inflammatory and benign lesions from early carcinoma becomes very important, especially in women susceptible to carcinoma of breast.

Most of the benign epithelial lesions are named by many pathologists with variety of terminologies such as cystic disease, fibrocystic disease, cystic mastitis, cystic mastopathy, epithelial hyperplasia, mammary dysplasia, and benign breast disease.[2] Besides, fine-needle aspiration cytology (FNAC) of breast, biopsies, and mastectomy specimens is frequently sent for histopathological examination (HPE). Many of the breast lesions are clinically suspected as malignant lesions but diagnosed as benign after HPE. The varied pattern of benign breast lesions draws our attention to study them in detail with the help of available clinical and radiological data. Since the most important prognostic factor at the time of presentation is the extent of the disease, it is imperative that a definitive preoperative diagnosis is established as early as possible with a view to institute proper treatment and reduces the mortality rates. In recent years, mammary cytology has been contemplated as an effective means of early diagnosis of breast masses.[3]

The combination of fine-needle cytology, clinical examination, and mammography has been suggested as a triple test for the pre-operative diagnosis of breast masses.[4] The advantage of these cytological procedures lies in the evidence that they are simple to perform, cost-effective, rapidly accepted by the patient, and cosmetically least disfiguring. This more rapid diagnostic approach assists to allay the anxiety caused by delays in scheduling, performing, and interpreting an open biopsy.

Cancer of breast is the most common cancer affecting women worldwide and is the second most common cause of cancer death next to lung cancer.[5]

It traditionally presents as a lump or nipple discharge.[6]

"Lump" in breast is, therefore, a cause of great anxiety both to the patient and family members. The main motive behind the evaluation of such a newly detected palpable lump is basically to rule out malignancy. Evaluation of breast lumps includes the rational use of a detailed history, clinical breast examination, imaging modalities, and tissue diagnosis. Although the final diagnosis is made by HPE of the excised tissue, routine excision of all breast lumps would not be rationale, because as much as 80% of lumps are benign.[7]

Thus the requirement of less invasive and cost effective method(s) of diagnosis without applying a more painful and invasive surgical biopsy. The modality should also be acceptable to the patient, accurate, easy to apply, reproducible and must not need too much preparations.[6]

Given the common occurrence of breast cancer and the importance of accurately diagnosing a clinically palpable breast lump, with non-invasive techniques without routinely resorting to formal biopsy which is much invasive, the study is proposed to evaluate the accuracy of ultrasonography (USG) and FNAC in the diagnosis of newly detected clinically palpable breast lumps in comparison to the final HPE report of the biopsied specimens.

Breast lumps are one of the common complaints/cases reported which necessitate early diagnosis, treatment, and work up. Breast cancer is the most constant among women with an estimated 1.67 million new cases diagnosed in 2012 (about 25% of total cancer). It is now the most common cancer in both developed (794,000 cases) and developing regions (883,000 cases). Incidence rate varies from 27 per lac women in Eastern Africa to 98 per lac women in Western Europe. The range of mortality rate is similar, approximately 6–20 per lac, because of the more favorable survival of breast cancer cases in developed countries. As a result, breast cancer rank as the fifth cause of death from cancer but it is still the most frequent cause of cancer death in women in developing regions.[8]

It is estimated that during the year 2012, about 144,937 new cases of breast cancer in women occurred in India, which accounts for 27% of all malignant cases (an incidence rate of 25.8 per lac population). About 70,218 women died of this cancer, mortality rate being 12.7 per lac population, ranking number one killer in women.[8]

A benign diagnosis allows surgery to be avoided in the majority of cases, while a positive diagnosis of carcinoma allows pre-operative discussion with the patient and proper treatment planning with minimal morbidity.[9]

Breast carcinoma is the leading cause of death in females all over the world. About 6% of all women may suffer from carcinoma breast at any point during their lifetime.[9] Carcinoma of the breast can present in several pathological forms across several age groups though it is a commoner there have been several areas of controversy surrounding its presentation and management.

Human chorionic gonadotropin (hCG) is a glycoprotein secreted by placental trophoblasts. Previous studies showed that hCG could be responsible for the pregnancy-induced protection against breast cancer in women. It is reported that hCG decreases proliferation and invasion of breast cancer MCF-7 cells. hCG can decrease the

proliferation of MCF-7 cells by downregulating the expression of proliferation markers, proliferating cell nuclear antigen, and proliferation-related Ki-67 antigen. Interestingly, we learn here that hCG elevates the state of cellular differentiation, as characterized by the upregulation of differentiation markers, β-casein, cytokeratin-18, and E-cadherin. Inhibition of hCG secretion or luteinizing hormone/hCG receptors synthesis can weaken the effect of hCG on the induction of cell differentiation. In addition to this, hCG can suppress the expression of estrogen receptor-alpha. hCG activated receptor-mediated cyclic adenosine monophosphate/protein kinase a signaling pathway. These findings are suggestive of a protective effect of hCG against breast cancer probably corresponding with its growth inhibitory and differentiation induction function in breast cancer cells.[10]

It is in this context that our study has been designed and carried out which will focus on the correlation of various diagnostic modalities which are prerequisites for early diagnosis and treatment of breast diseases and correlation of beta hCG with breast diseases. Appropriate literature review and analysis using standard statistical tests would be used to arrive at conclusions, the details of which are mentioned below.

MATERIALS AND METHODS

The protocol was approved by the local ethics committee and written informed consent was obtained from each patient. This is a prospective observational study consisting of 112 patients with breast diseases planned for surgical management from June 2016 to June 2018 and a cyto-sono-histopathological correlation done. Pre-operative evaluation included history, clinical examination, USG breast, serum beta-hCG, and post-operative histopathology.

Table 1: Age-wise distribution of cases

Age group (in years)	Number of cases	Percentage
14–25	40	35.7
25–35	18	16.1
35–45	26	23.2
45–55	14	12.5
55–65	8	7.1
>65	6	5.4
Total	112	100.0

RESULTS

Results and Analysis

To ensure uniformity in the diagnostic reporting, The National Cancer Institute (NCI) (NHS Breast Screening Programme 2001)[11] has developed and recommended five categories for assessing and reporting of palpable breast lesions. The five categories for reporting of these lesions are: Inadequate smear (C1), benign (C2), suspicious probably benign (C3), suspicious probably malignant (C4), and malignant (C5).

The statistical analysis showed high sensitivity (87.5) and specificity (100%) of FNAC in breast lesions, with positive predictive value (PPV) and the negative predictive value (NPV) being 100% and 95.4%, respectively. The diagnostic accuracy was found to be 96.5%.

The statistical analysis showed high sensitivity (84.8) and specificity (96.5%) of FNAC in breast lesions, with PPV and the NPV being 90.3% and 94.3%, respectively. The diagnostic accuracy was found to be 93.3% [Tables 1-15].

DISCUSSION

FNAC of breast lumps is an accepted and established method for determining the natures of breast lumps with a high degree of accuracy.[12,13] Application of FNA for the diagnosis of palpable breast masses was first introduced by Martin and Ellis in 1930, and since then, it has been established as an important tool in the evaluation of breast lesions.[4] It has been reported in the literature that the incidence of tumor transplantation along the needle track by FNA procedure is only about 0.0045%, and even much lower in superficially located tumors.[14] FNA is widely accepted as a reliable technique in the initial

Table 2: Distribution of benign and malignant cases according to age groups

Age group (in years)	Number of cases (benign)	Percentage	Number of cases (malignant)	Percentage
11–20	19	17	0	0
21–30	29	25.89	0	0
31–40	25	22	3	2.68
41–50	7	6.25	8	7.14
51–60	2	1.79	12	10.71
61–70	1	0.89	4	3.57
Above 70	1	0.89	1	1.79
Total	84	75.00	28	25.89

Table 3: Gender-wise distribution of cases

Sex	Number of cases	Percentage
Male	5	4.5
Female	107	95.5
Total	112	100

Table 4: Site of breast involved among the cases

Site involved	Number of benign	Number of malignant	Number of cases	Percentage
Left breast	29	15	44	39.3
Right breast	46	13	59	52.7
Bilateral	9	0	9	8.0
Total	84	28	112	100

Table 5: Type of quadrant involved among the cases

Quadrant involved	Number of cases	Percentage
Upper outer	51	45.5
Upper inner	18	16.1
Lower outer	13	11.6
Lower inner	11	9.8
Central	13	11.6
Diffuse	6	5.4
Total	112	100

Table 6: Tumor size-wise distribution of cases

Tumor size (in cm)	Number of cases	Percentage
1–2	3	2.6
2–5	87	77.7
5–10	17	15.2
>10	5	4.5
Total	112	100

Table 7: Cytological spectrum of breast lumps on fine-needle aspiration cytology

Cytological diagnosis	Number of cases	Percentage
C1 (inadequate)	9	8
C2 (benign)	75	67
C3 (atypia probably benign)	4	3.57
C4 (suspicious probably malignant)	6	5.35
C5 (malignant)	18	16.1
Total	112	100

evaluation of palpable breast lumps. It is simple, safe, cost-effective, minimally invasive, rapid, and as sensitive as biopsy[15-17] primary goal of FNA is to separate benign lesions from malignant lesions for the purpose of planning the therapeutic protocol and uneventful follow-up.[18-20] In the present study, 300 cases were studied and cytological examination was done using 22 or 24 gauge disposable needles, measuring 1.5" in length and 10 ml disposable syringes without holders.

Table 8: Distribution of malignant lesions

Cytological diagnosis	Number of cases	Percentage *n*=112
Suspicious of malignancy (C4)	6	5.35
Ductal carcinoma *in situ* (C5)	15	13.3
Invasive ductal carcinoma-not otherwise specified (C5)	3	2.67
Total	24	21.32

Table 9: Radiological spectrum of breast lumps on sonography

Sonological diagnosis birads	Number of cases	Percentage
0 (incomplete)	0	0
I (normal)	1	0.89
II (benign)	67	59.8.
III (probably benign)	14	12.5
IV (suspicious abnormality)	18	16
V (malignant)	11	9.8
VI (proven malignant)	1	0.9
Total	112	100

Age and Sex Distribution of Cases

In the present study, the age of the patients ranged from 14 to 85 years with mean age of 38.93 years (standard deviation-16.32). The study population comprised 107 female and 5 male cases. The oldest case (85 years) was diagnosed as gynecomastia and the youngest (15 years) was a fibroadenoma. The most common age group was 31–40 years comprising 83 cases (27.7%). In this study, the maximum numbers of cytologically benign lesions were seen in the age group ranging from 11 to 40 years. In the present study, the range of age of the breast carcinoma cases was 25–70 years. We observed a maximum incidence of breast cancer in the age group of 41–50 years (37.1%). Above 60 years, it was 10% and only 8.6% between 21 and 30 years. Between the age group of 31 and 40 years and 51 and 60 years, frequency of breast cancers is 22.5% and 21.4%, respectively. This is similar to study done by Afsharfard *et al.*[21] and Chopra *et al.*[22]

This was similar to the findings by Khemka *et al.*[22] and Rocha *et al.*[23] who had maximum cytological benign cases in the age groups of 15–44 years and 14–40 years, respectively. MacIntosh *et al.*[24] had majority of benign cases in the age group of 27–77 years. Malignant lesions were common in the age group of 31–70 years in the present study, 35–84 years in the study by Khemka *et al.*[22] 63–79 years in the study by MacIntosh *et al.*[24] and 41–75 years in the study by Rocha *et al.*[23] Hence, overall pattern of occurrence is as expected, with benign lesions were more common in younger age group and malignant lesions in older age group. Similar age group distribution of benign and malignant cases was observed in studies done in Asian countries.[24,25] Higher age group in Western countries was attributed to higher life

Table 10: Summary of statistical analysis of cytology

Cytological diagnosis	Histopathogical diagnosis		Total	*P*-value by Chi-square
	Malignant (positive)	Benign (negative)		
Positive for malignancy (malignant)	24 (TP) (a: True positive)	0 (FP) (b: False positive)	25	<0.05
Negative for malignancy (benign)	4 (FN) (c: False negative)	84 (TN) (d: True negative)	87	
Total	28	84	112	

True positive cases (TP)=24 False positive cases (FP)=00, True negative cases (TN)=84 False negative cases (FN)=04

$$\text{Sensitivity} = \frac{TN}{TP+FN} \times 100 = \frac{24}{24+04} \times 100 = 85.7\%$$

$$\text{Specificity} = \frac{TN}{TN+FP} \times 100 = \frac{84}{84+0} \times 100 = 100\%$$

$$\text{Positive predictive value} = \frac{TP}{TP+FP} \times 100 = \frac{24}{24+00} \times 100 = 100\%$$

$$\text{Negative predictive value} = \frac{TN}{TN+FN} \times 100 = \frac{84}{84+4} \times 100 = 95.4\%$$

$$\text{Accuracy} = \frac{TP+TN}{TP+FP+FN+TN} \times 100 = \frac{24+84}{24+0+4+84} \times 100 = 96.4\%$$

Table 11: Statistical results of cytology

S. No.	Statistical indices	Result (%)
1.	Sensitivity	87.5
2.	Specificity	100
3.	Positive predictive value	100
4.	Negative predictive value	95.4
5.	Diagnostic accuracy	96.5

expectancy.[26] Khemka *et al.*[22] observed that benign lesions of breast were more commonly seen in younger age groups with maximum number of patients found in the age group of 30–34 years. Ganiat *et al.*[25] reported a maximum number of patients with malignant lesions in the age group from fourth to seventh decade of life.

In India, the average age of developing breast cancer has shifted over the past few decades and younger women (40–50 year) are being affected. Epidemiological studies suggest that this cancer occurs at a younger premenopausal age in Indian and Asian women compared to western women who get it more than a decade or more later.

The lifestyle factors such as late age at marriage, reduced breast feeding, and westernization of diet may be associated with occurrence of breast cancer in younger population in India. Early menarche and late menopause also increase risk of disease. India may face a potential breast cancer epidemic over the next decades as women adopt western lifestyles, marrying, and bearing children later in life, decreasing parity, shorter duration of breastfeeding, and change in dietary habits.[21]

Most of cases (98.6%) were females. Only five case male but all of them are benign. No male breast cancer found in this study period, this finding somewhat is similar to Shet *et al.*[27] who found 1.6% of male breast cancer in total breast cancer cases.

Breast cancer is about 100 times less common among men than among women. For men, the lifetime risk of getting breast cancer is about 1 in 1000.

Site and Location of Breast Involvement among the Cases

In our study, 68.6% cases had left side breast cancer and 31.4% cases had right side breast cancer, which is similar to studies by Moses Ambroise *et al.* who reported 59.2% cases in left breast. The observation that breast cancer is more common in the left than the right breast has been of interest to the medical community for at least 50 years. A satisfactory explanation for the excess incidence of left breast cancers has not yet been elucidated.

In our study, most common location involved was upper outer quadrant (57.1%). Second common location was subareolar (32.9%), followed by lower inner, lower outer, upper inner 5.7%, 2.9%, and 1.4%, respectively. This is similar to study done by Lee.[28]

The marked difference in the carcinoma frequency depending on the quadrant matches closely to the amount of breast parenchyma in each quadrant.

Out of 112 cases studied, 44 cases (39.3%) were in left breast, 59 cases (52.7%) were in right breast, and 9 cases (8%) presented bilaterally. Hussain[25] reported left breast involvement in 27 patients (54%) and right breast involvement in 23 cases (46%) and concluded that left breast was involved more commonly than right. Meena *et al.*[29] Reddy and Reddy,[30] and Clegg-Lamptey and Hodasi[31] also studied that palpable breast lesions on the left side were slightly more common.

Among all four quadrants, upper and outer (superolateral) quadrant was the most commonly involved quadrant (54.33%) in the present study with 112 cases. This is in agreement with the findings of other studies such as Rocha *et al.*[32] (45.20%), Zuk *et al.*[33] (42.20%), Reddy and Reddy *et al.*[30] (54.20%), Meena *et al.*[29] (54%), and Clegg-Lamptey and Hodasi *et al.*[31] (42.40%). The exact cause of this finding is not known. Hussain *et al.*[15] and Khemkha *et al.*[11] also

Table 12: Summary of statistical analysis of Sonology

Sonological diagnosis	Histopathogical diagnosis		Total	*P*-value by Chi-square
	Malignant (positive)	Benign (negative)		
Positive for malignancy (malignant)	28 (TP) (a: True positive)	03 (FP) (b: False positive)	31	<0.05
Negative for malignancy (benign)	5 (FN) (c: False negative)	84 (TN) (d: True negative)	89	
Total	33	87	150	

True positive cases (TP)=28 False positive cases (FP)=03, True negative cases (TN)=84 False-negative cases (FN)=05

$$\text{Sensitivity} = \frac{TP}{TP+FN} \times 100 = \frac{28}{28=05} \times 100 = 84.8\%$$

$$\text{Specificity} = \frac{TN}{TN+FP} \times 100 = \frac{84}{84+03} \times 100 = 96.5\%$$

$$\text{Positive predictive value} = \frac{TP}{TP+FP} \times 100 = \frac{28}{28+03} \times 100 = 90.3\%$$

$$\text{Negative predictive value} = \frac{TN}{TN+FP} \times 100 = \frac{84}{84+5} \times 100 = 94.3\%$$

$$\text{Accuracy} = \frac{TP+TN}{TP+FP+FN+TN} \times 100 = \frac{28+84}{28+03+05+84} \times 100 = 93.3\%$$

Table 13: Statistical indices of sonography

S. No.	Statistical indices	Result (%)
1.	Sensitivity	84.8
2.	Specificity	96.5
3.	Positive predictive value	90.3
4.	Negative predictive value	94.3
5.	Diagnostic accuracy	93.3

observed upper and outer quadrant as the commonest site. Swapan and Ranjana.[34] determined the topographic distribution of different breast lesions and observed that the left breast was found to be more common site of malignancy and the upper outer quadrant being the most common site.

All the 112 aspirations were subjected to cytological study lesions were classified into five diagnostic classes, to ensure uniformity in the diagnostic reporting, the NCI has developed and recommended five categories for assessing and reporting of palpable breast lesions.[35] The five categories for reporting of these lesions are: Inadequate smear (C1), benign (C2), atypia probably benign (C3), suspicious probably malignant (C4), and malignant (C5).

In the present study of 112 patients, 84 cases were benign cases (76.66%), and malignant lesions were found in 28 cases (21%). Yeoh and Chan[36] studied 1533 breast masses on FNAC and found that 70.4% cases were benign. Similarly, Ganiat *et al.* studied 757 cases on FNAC and found that maximum number of cases was benign (50.2%), Malik *et al.*[36] in his study of 1724 cases over a period of 20 years reported benign lesions in 72.97% and malignant lesions in 27.3% of cases. Similar results were obtained by Iyer[37] and Mayun *et al.*[38] A difference was noted in the incidences of benign and malignant breast lesions amongst various studies, which may be explained on the basis of variables such as the duration of study period, number of cases studied, and age group of patients.

It has been emphasized in the past that vast majority of the lesions in breast are benign.[39-42] Aslam *et al.*[43] also documented fibroadenoma as the most common benign lesion (71.3%) in their study. López-Ferrer *et al.*[44] stated that FA may be accompanied by changes such as atypical multinucleated giant cells and mild epithelial atypia, which may lead to an erroneous diagnosis of malignancy.

Another common benign breast lesion we encountered was fibrocystic change with 2 cases (1.7%) which was characterized by sheets of ductal epithelial cells of apocrine type and scattered single bipolar nuclei in the background of variable amount of cyst fluid and macrophages. More than 90% of the fibrocystic change were non-proliferative. Compared to the general population, proliferative fibrocystic change with or without atypia has relative risk of developing carcinoma. Other benign and cystic lesions encountered were simple benign cysts with 1 cases (0.89%), gynecomastia 5 cases (4.4%), and benign phyllodes tumor 2 cases (1.7%). Inflammatory lesions accounted for 3 cases (2.7%), which included cases of chronic inflammatory cells along with ductal epithelial cells showing regenerative atypia, 1 cases of granulomatous mastitis, and 1 cases of chronic mastitis. In the present study, 1 case (5.66%) showed epithelial hyperplasia, 2 cases of lipoma, fat necrosis, and duct ectasia each. Six cases of breast lump on cytology showed lactational changes and 1 case of duct papilloma was also seen in the study population.

Breast cancer is the second most common cancer among Indian females next only to cervical cancer. In experienced hands, FNA is highly accurate diagnostic procedure with sensitivity and specificity over 95% for palpable breast lesions.[45,46] In the present study, 18 cases (16.1%) were positive for malignancy with maximum incidence of carcinoma and were found in 51–60 years (12 cases). Out of 18 malignant lesions, 15 cases were diagnosed as ductal

Table 14: Comparison of cytological findings of the present study with the various other studies

Studies	Total cases	Benign cases, *n* (%)	Atypical cases, *n* (%)	Malignant cases, *n* (%)	Suspicious cases, *n* (%)	Unsatisfactory cases, *n* (%)
Feither *et al*.[76]	1472	1003 (68.1)	12 (0.8)	239 (26.6)	169 (11.5)	49 (3.3)
Khan *et al*.[77]	74	24 (32.4)	03 (4.1)	41 (55.4)	06 (8.1)	0 (0)
Yusuf *et al*.[78]	200	109 (54.5)	20 (10)	44 (22)	27 (13.5)	0 (0)
Panjvani *et al*.[53]	222	150 (68.18)	01 (0.45)	69 (31.08)	02 (0.90)	00 (00)
Chokshi *et al*.[79]	407	293 (22.59)	08 (1.96)	70 (17.19)	08 (1.96)	28 (6.87)
Present study	112	75 (67)	4 (3.5)	18 (16.1)	6 (5.35)	9 (8)

Table 15: Comparison of overall diagnostic accuracy of FNAC in breast lesions

S. No.	Study	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
1.	Silverman *et al*.[80]	96	100	100	98	99
2.	Sampat *et al*.[81]	96	100	100	89.5	97
3.	Rocha *et al*.[23]	93.80	98.21	92.70	95.6	97.4
4.	Choi *et al*.[82]	77.7	99.2	98.4	88	91.1
5.	Pinto *et al*.[58]	97.8	100	100	98.6	99.1
6.	Joshi *et al*.[83]	96.97	100	100	98.63	99.1
7.	Present study	87.5	100	100	95.4	96.5

FNAC: Fine-needle aspiration cytology

Table 16: Distribution of breast lesions

Category	Histopathological diagnosis	Number of cases	Percentage *n*=112
Inflammatory lesions (3 cases-2.7%)	Zuska disease	1	0.89
	Granulomatous mastitis	1	0.89
	Chronic mastitis (non-specific)	1	0.89
Benign breast lesions (72 cases-61.24%)	Fibroadenoma	62	55.3
	Fibrocystic change	2	1.7
	Tubular adenoma	2	1.7
	Simple cyst	1	0.89
	Epithelial hyperplasia	1	0.89
	Gynecomastia	5	4.4
Lesion not recognized as benign or malignant	Phyllodes tumor	2	1.7
Miscellaneous	(Lipoma, keratin cyst)	6	5
Carcinoma		28	25
Total		112	100

carcinoma. Singh *et al*.[47] reported that invasive ductal carcinoma is the most common breast malignancy and found in the age group of 41–60 years of age.

Out of 112 cases studied for cytology, histopathology was available for 112 cases which were operated in K.J. Somaiya Hospital. Of the 18 FNAC positive for malignancy cases, the histopathology follow-up of 18 cases was available as only these patients underwent surgery for breast cancer in this institute. (We took only patient which underwent surgery).

In the present study, there were 88 cases diagnosed under the benign category from which 88 cases were available for histological follow-up. Out of these 88 confirmed cases, 84 cases were found to be benign while four case was found to be malignant (false-negative case). One false-negative case which was seen in the lactating female whose cytology was diagnosed as giant fibroadenoma, its further follow-up on histopathology was found out to be infiltrating ductal carcinoma.

The false-positive FNAC results can be reduced by considering biopsy in such cases, especially when the aspirate yields poor cellularity shows presence of bare nuclei and lesser degree of atypia.[48]

In this prospective study, 112 cases were included for cytohistologic correlation with 88 (78.5%) benign cases, 18 (16%) malignant cases, and 6 (5.3%) cases reported as suspicious of malignancy. Among the benign cases fibroadenoma comprised the maximum cases (35) followed by breast carcinoma in 24 cases. In the present study, 6 cases which were cytologically diagnosed as lesions suspicious for malignancy, of which 6 were confirmed as malignant lesions on HPE, however. No case was diagnosed as benign. Cytohistologic correlation was seen in 95.4% of benign cases and 100% in cases suspicious for malignancy.

All the 18 cytologically diagnosed malignant cases were confirmed as malignant on subsequent HPEs. Hence, in our study, a 100% cyto-histopathological correlation was observed for malignant lesions Qin *et al*.[49]

AZ Mohammed *et al*.[50] and Tiwari[6] had also observed the similar results in their studies. Other studies also noted an increase in rate of malignancy on histopathology in lesions which were previously diagnosed under the category of "suspicious lesions for malignancy." Comparison of cytohistological correlation in various studies is shown in Table 16.

Suen and Chan *et al*.[51] in their study stated that the PPV for malignancy should be >95% with a false-positive rate of <1% and false-negative rate of <5%. In present study, the PPV for malignancy was 100% with no false-positive case which meets the criteria mentioned by Suen.

Bell *et al*.[52] had stated that aspiration cytology was accurate, rapid and of value in the assessment and management of patient in office practice. Documentation of the presence of breast cancer by FNAC might obviate the need for a two stage procedure in the surgical management of breast cancer. In our institution also FNAC is being used as basic test for surgical management of malignant breast lesions; after surgery the whole specimen is submitted for HPE and confirmation of malignancy.

Panjvani *et al*.[53] studied 222 patients, 217 were females and 5 were males. Benign breast lesions were found in 144 cases (64.87%); among which fibroadenoma (30.18%) was the commonest lesion which was observed. Malignancy was observed in 69 cases (31.08%); among them, infiltrating ductal carcinoma was the predominant lesion (29.28%) which was seen. Histopathological confirmations were obtained in 91 cases, in which histocytopathological corrections were possible. All 45 malignant aspirates were confirmed by histopathology. Benign reports were confirmed in 45 out of 46 cases by doing histological examinations; except one case which was diagnosed as malignant by studying its histopathology. Sensitivity and specificity of FNAC in breast lesions were reported to be 97.82% and 100%, respectively, with 100% PPV and 97.85% NPV.

Diagnostic accuracy of FNAC in the present study was found to be 98.9%. These findings were comparable to the findings in our study.

Monika *et al*.[54] studied that a total of 128 cases were studied which included 101 benign cases, 21 malignant cases, and 6 inadequate cases. The final 122 cases included, 44 cases (36.1%) of fibroadenoma, there were 21 cases (17.21%) of ductal carcinoma. Majority of benign cases were between 30 and 39 years of age group (43.6%). Majority of malignant cases fell between 50 and 59 years of age group (47.6%). Majority (61.5%) of lumps (>3 cm) were malignant, whereas 94.8% of lumps (<3 cm) were benign. Left breast was commonly involved (49.18%) than the right breast (44.26%). Superolateral quadrant (63.1%) was the most commonly involved quadrant. The findings were similar to the findings in our study.

Halevy *et al*.[55] have stated that to achieve good results, three rules must be borne in mind. First, a trained cytopathologists should perform the FNAC and interpret the result. Second, close cooperation between surgeon and cytopathologists is necessary. Finally, a negative FNAC finding does not rule out a malignant condition.

Yeoh and Chan[36] in their study reported six cases as false negative which include one heavily blood stained smear that had mixed cytological features, which was interpreted as a cyst, two misdiagnoses due to well differentiated tumors in the benign category, and three cases that were reported as atypical. False-negative diagnosis might be due to technical failure, misdiagnosis, or the presence of mixed benign and malignant cytological features. Technical failure include acellular or insufficient cellular material, heavily blood stained smears, partial air drying, and smearing artifact resulting in cell disruption.

Ariga *et al*[56] performed 1158 FNAs on women being evaluated for a clinically palpable breast masses. The patients were divided into two groups. Group I consisted of 231 patients aged 40 years and younger and Group II consisted of 927 patients aged 41 years and older. In Group I, there were 117 (51%) malignant FNA diagnosis and only 1 (1%) false-positive case, subsequently diagnosed on histopathological material as an atypical papillomatosis. There were 20 (9%) cases diagnosed as suspicious on FNA. On histopathology, 10 were malignant and 10 were benign. Of the 91 (3%) cases interpreted as benign, only one was false-negative. In Group II, which comprised 927 patients, there were 693 (74%) malignant FNA diagnosis and 3 (<1%) false-positive cases, which on follow-up HPE revealed two atypical ductal hyperplasia and one atypical papilloma. For cases suspicious on FNA, 90 (10%) were diagnosed. On histopathology, 68 were malignant and 22 were benign. Of the 131 (14%) lesions interpreted as benign, there were 18 false-negative cases (14%) which included 17 infiltrating carcinomas and one DCIS. For the study, 12 (1%) cases were inadequate. Group I had 99% sensitivity, 99% PPV, 99% specificity, 99% NPV. Group II had 98% sensitivity, 97% specificity, 99% PPV, and 86% NPV. These results were comparable with the results of our study.

Ishita *et al*.[57] performed 125 FNAs of breast over a period of 1 year. Of these 60 cases were followed-up by

histopathologic confirmation. The diagnostic accuracy of this series was assessed. The sensitivity of the FNA procedure was 93.10%, specificity 97.06%, with a PPV 96.43%. The overall diagnostic accuracy was 95.24%. The present study shows comparable results with sensitivity 98.3%, specificity 98.9%, and diagnostic accuracy of 98.7%.

Pinto *et al.*[58] did 58 FNAs of the breast with subsequent histopathology. The youngest patient was 12 and the oldest was 82. Females comprised 555 (95.4%) and males 27 (4.6%). Out of 582 aspirations, 295 cases (50.7%) were negative (benign) on cytology and in 107 cases (18.4%) the smears were inconclusive and biopsy was advised. Fibroadenoma (188 cases) was the most common benign neoplasm. The cytohistologic correlation was 89.7% for fibroadenoma, 65.2% for fibrocystic change, 60% for benign phyllodes tumor, 57.1% for fibroadenosis, and 33.3% for breast abscess.

The present study confirms the view that FNAC has high ability to detect benign and malignant lesions with high efficacy and accuracy. Thus, FNAC of breast is a sensitive and specific modality in diagnosing breast lesion and in management of the breast lesions.

Breast carcinoma has been reported in only 4% of patients with breast symptoms, and even among palpable lesions undergoing biopsy, a large number of lesions turned out to be benign.[59,60] The role of mammography in patients with palpable breast lumps is to show a benign cause for palpable abnormality and to avoid further intervention, to support earlier intervention for a mass with malignant features, screen the remainder of the ipsilateral and contralateral breast for additional lesions, and to assess the extent of malignancy when cancer is diagnosed.[61] However, the false-negative rate of mammography for breast cancer in patients with palpable abnormalities of the breasts has been reported to be as high as 16.5%.[62] Multiple studies have shown that the false-negative rate for a combined mammographic and sonographic evaluation varies from 0% to 2.6%.[63,64] Additional imaging with sonography is appropriate in most instances, with the exception of lesions that are mammographically benign as noted above or lesions that are highly indicative of malignancy, in which sonographic imaging would not add any additional information. Sonography may obviate the need for intervention by showing benign causes of palpable abnormalities such as cysts, benign intra mammary lymph nodes, extravasated silicon, and superficial thrombophlebitis of Mondor disease of the breast.

In this study, 20 (40%) of the 50 lesions were categorized as benign after sonographic evaluation, clearly showing the value of imaging in helping avoid unnecessary biopsies. In these patients, sonography was able to categorize palpable lesions obscured by dense tissue on mammograms. Moss *et al.*[51] reported that sonography increased cancer detection by 14% in symptomatic patients who were evaluated with both mammography and sonography. In retrospective analysis of 293 palpable malignant lesions, sonography detected all cancers; 18 (6.1%) of these 293 cancers were mammographically occult. In study of 411 palpable abnormalities by Shetty and Shah, 66 (16%) of the 165 palpable abnormalities were mammographically occult. In this study, one lesion (fat necrosis) was sonographically occult and was visualized only on mammography. Seven (14%) of the 50 lesions were mammographically occult and were seen only on ultrasound. Of these 6 were benign cysts and one was duct ectasia. Sonography therefore is complimentary to mammography in patients with palpable abnormalities; its superiority over mammography is in being able to show lesions obscured by dense breast tissue and in characterizing palpable lesions that are mammographically visible or occult. Mammography is complimentary to sonography because of its ability to screen the reminder of the ipsilateral and contra lateral breast for clinically occult lesions. It has been reported that the accuracy of sonography is comparable with that of mammography as a screening modality for breast cancer. However, the role of sonographic screening for additional lesions in the symptomatic patients has not been reported.

Combined imaging evaluation leads to fewer unnecessary biopsies. Perdue *et al.*[60] reported that only 11.1% of 623 excisional biopsy specimens of palpable breast revealed carcinoma.[39] In this study, only 7 of the 50 palpable abnormalities underwent biopsy on the basis of imaging findings and only 2 (4%) showed malignancy.

In a review article, Donegan[57] stated that most of the breast cancers appear as palpable masses, usually found by the patient. However, not all palpable abnormalities represent discrete masses. This is especially true in women younger than 40 years in whom normal glandular nodularity may be mistaken for dominant masses.[65] In this study, 50 patients who presented with palpable abnormalities 23 patients showed negative findings sonographic examination. Nine of these patients underwent biopsy on the grounds of clinical suspicion and all were benign. Of 411 palpable abnormalities studied by Shetty and Shah 186 cases showed negative findings, clearly showing the importance of imaging.

A small number of palpable masses detected on physical examination are malignant; in this study, 4% of the palpable lesions that underwent combined mammographic and sonographic imaging were cancer, compared with 5% in a series of 123 cases of palpable breast thickening reported by Kaiser *et al.*, 5% in 605 patients younger than 40 years

reported by Marrow *et al.*, and 17% in 750 breast lesions reported by Stavros *et al.*

The value of combined mammographic and sonographic imaging in symptomatic patients has been studied previously. Moss *et al.* reported sensitivity of 94.2% and specificity of 67.9% in 368 patients. Shetty and Shah reported a sensitivity of 100% and specificity of 80.1%. Barlow *et al.* reported a sensitive of 87% and specificity of 88% and PPV of 22%.[66]

Their findings are comparable with present findings of sensitivity of 84.8% and specificity of 96.5% in patients with palpable breast lumps.

Heterodimeric placental HCG and ectopically expressed β-HCG have opposing effects on breast cancer development. The reasons for these contrary effects are still controversial. One explanation could be the glycosylation state of HCG, finding that hyperglycosylated β-subunits of HCG promote cancer cell invasion, growth, and metastases. Another cause for the differing effect of HCG on breast cancer cells could be the fact that the *LHCGR* carries a large number of polymorphisms. As a consequence, sensitivity and plasma membrane expression can be changed, leading to different receptor activity. Moreover, *HCG* genes also carry many polymorphisms which lead to expression of different HCG types. All these points can cause opposing effects on breast cancer development and could explain controversial data at least partially. The protective effect of placental HCG on the mammary gland led to the hypothesis that mimicking pregnancy might be a strategy for breast cancer prevention. In contrast, the tumor-promoting β-HCG expressed in breast cancer cells seems to be a promising target for immunological approaches of breast cancer therapy.[67]

The majority of previous studies clearly suggests a protective or inhibitory action of heterodimeric placental HCG on breast cancer development, though other studies could not find such an effect. In animal models, administration of hCG reduced risk of carcinogen-induced breast cancer, an effect which was mediated by induction of apoptosis and elevated inhibit expression.[68-70]

Various studies reported a negative correlation between serum HCG levels and breast cancer risk. Russo *et al.* found that high levels of HCG during the 1st weeks of pregnancy reduced the incidence of maternal breast cancer rate after the age of 50.[71] Toniolo *et al.* reported a risk reduction of about 30% of getting breast cancer when women had higher HCG levels in the first 3 months of pregnancy.[72] Lukanova *et al.* found that women with HCG levels in the top tertile tended to be at lower risk of breast cancer than women with HCG levels in the lowest tertile.[73] No such inverse relationship between early pregnancy serum HCG concentrations and breast cancer risk was found by other studies including in a recent large prospective study from Finland including 1191 women with invasive breast cancer and 2257 controls.[74] In another study, young nulliparous women receiving injections of HCG for weight loss or infertility treatment were reported to have a slightly decreased risk for developing breast cancer.[75]

The beneficial effect of HCG was supported by the results of two studies examining the effect of treatment with recombinant HCG. In a placebo-controlled study, postmenopausal women with primary breast cancer diagnosed by core biopsy were treated with HCG or a placebo for 2 weeks. After this period, therapeutic mastectomies or lumpectomies were performed. Tissue examinations demonstrated that the proliferative cell index was decreased from 18% to 4% in the HCG-treated group, suggesting that this hormone is able to inhibit breast cancer cell proliferation.[49]

Contradictory to other studies we found that there is no correlation of serum beta-hCG with breast diseases. Serum beta-hCG neither protective nor promotive factor for breast disease

CONCLUSION

Use of sonography plays an important role in the management of palpable breast lesions. Its applications are.

- Characterizes the palpable mass lesion.
- Avoids unnecessary interventions in which imaging findings are unequivocally benign.

Negative findings on sonographic imaging have very high specificity and are reassuring to the patient.

FNAC is a patient friendly, easy, reliable, repeatable, and simple diagnostic test. When performed by an expert pathologist, the diagnostic accuracy of FNAC is very high. A high sensitivity and a high PPV proved that a positive FNAC in the breast means a definite diagnosis of the concerned pathology if compared with the final histology report. The high specificity and a high NPV for malignancy illustrated the high accuracy of FNAC in the diagnosis of malignancy in the breast. Very importantly, a report negative for malignancy was highly accurate (>98%) in predicting an absence of malignancy. Thus, we conclude that FNAC is a very important preliminary diagnostic test in palpable breast lumps. Adhering to the principle of triple test, with the acquisition of technical, observational, and interpretative skills will further enhance the diagnostic

accuracy of lesions of the breast.

Over all our study concludes that sonography should be the first investigation to be done after clinical examination because if sonography says disease is benign then patient can be assured without any invasive procedure, i.e., FNAC and biopsy. If sonography says abnormality then patient should go for invasive procedure. As far as, for early definitive diagnosis FNAC is superior to Sonology. Serum beta-hCG has no correlation with breast diseases.

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Original Article

Evaluation of the Role of Circumcision in Reducing Symptomatic Urinary Tract Infection Following Posterior Urethral Valve Ablation

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Abstract

Aim: The aim of this single center short-term prospective study is to determine the effects of circumcision in reducing the risks of symptomatic urinary tract infection (UTI) in post posterior urethral valve (PUV) ablated patients and to compare them with their non-circumcised counterparts.

Objective: The specific objective of this study in the group includes: a. To identify patients with PUV who develop UTI with subsequent renal damage. b. Proportion of children with symptomatic UTI in each group. c. Relative risks of presenting with symptomatic UTI after PUV ablution and. d. To analyze statistically when circumcision really reduces the incidence of UTI in valve ablated patients.

Materials and Methods: A single institutional prospective study of patients who were admitted with PUV between April 2016 and September 2017 Institutional Ethics Committee Clearance and informed consent of the parents were taken. Boys with congenital anomalies along with hypospadias and epispadias or any other condition rendering circumcision impossible were excluded from the study.

Results: We identified 38 patients in all of whom 23 underwent circumcision at the time of valve ablation. The mean age of these patients was 41.22 days on a mean follow-up period of 1 year. Only one patient (4.35%) in the circumcised group had two episodes of UTI, whereas three patients (20%) who had not undergone circumcision had five episodes of UTI.

Conclusion: Circumcision along with PUV ablation does protect these patients from post-ablation symptomatic UTI and thus is protective against ongoing renal damage.

Key words: Circumcision, Urinary tract infection, Posterior urethral valve

INTRODUCTION

Posterior urethral valve (PUV) is the most common urethral anomaly that causes bladder outlet obstruction in male child.[1] The incidence ranges from 1 in 5000 to 1 in 8000 male births.

Although majority of the diagnosis is made in the antenatal period about 24%–45% of the patients suffer from renal insufficiency during childhood or adolescence and require transplantation within their first 18 years of life.[1,2]

The patients with PUV are prone to develop recurrent urinary tract infections (UTI) because of multiple causes, namely, vesicoureteric reflux, vale bladder, and subvesical obstruction[3] with or without bladder neck hypertrophy.

It has been widely accepted that circumcision prevents UTI through there are controversies regarding the age of operation and risk profile of the patients.[4]

Our study aims to find a correlation between the risk and incidence of symptomatic UTI in post ablated cases of PUV and compare it with those who did not undergo circumcision following vale ablation.

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MATERIALS AND METHODS

Single institutional prospective study was carried out between April 2013 and September 2014 with informed consent from the parents and approval of the ethical committee. Patients were selected consecutively with the inclusion criteria of the patients with PUV.

Inclusion Criteria

Boy diagnosed with PUV within the first 3 years of life.

Exclusion Criteria

Boys with various phallic anomalies such as hypospadias or epispadias which renders circumcision impossible were excluded in the study.

Surgical Technique

Cystoscopic vale ablation (at 5'O', 7'O', and 12'0' clock position) with bladder neck incision in appropriate cases following circumcision was performed under general anesthesia with per-operative antibiotic coverage (coamoxiclav) which was continued for 3–5 days postoperatively.

Rapidly absorbable polyglactin 910 suture was used for hemostasis and patients were put on the catheter.

We follow-up protocol consists of

a. Voiding cystourethrogram (VCUG) 3 months post vale ablation
b. Serial estimation of serum urea, creatinine, and routine microscopic examination of urine at monthly intervals for 3 months followed by 3 monthly interval for the next 5 years
c. US of the kidney, ureter, bladder along with an estimation of post-void residue every 6 months for 3 years and thereafter annually for 20 years
d. Urodynamic study in all cases emphasizing on bladder compliance and PdetQmax.

Drainage of the bladder from 3 post-operative days, no dressing was applied.

Patients were followed up in the outpatients department. Parents were specifically asked to report immediately if their wards suffer from any of the following conditions.

a. High rise of temperature
b. Crying during micturition
c. Turbid urine
d. Hematuria
e. Dysuria or any other symptoms pertaining to UTIs. Patients suffering from UTI were admitted and started on broad-spectrum antibiotics pending urine culture sensitivity report and associated resuscitative measures were taken. Parenteral antibiotics once stared were continued for at least 7–10 days and later shifted to oral medications until the urine becomes sterile. Thereafter chemoprophylaxis was continued till the upper tract dilation improves, which may take several years.

Table 1: Age distribution of patients who had undergone circumcision along with PUV ablation

Age in days	Total number of patients
0–60	16
60–180	5
>180	2
Total	23

PUV: Posterior urethral valve

Table 2: Mode of diagnosis in patients with PUV

Method	Number of patients	
Antenatal US	Circumcised	Un circumcised
	14	6
Post-natal US	21	12
VCUG	22	13
Cystoscopy	23	15

PUV: Posterior urethral valve, VCUG: Voiding cystourethrogram

RESULTS

Thirty-eight patients of PUVs were admitted to the study group. Twenty-three underwent circumcision at the time of valve ablation which 15 did not. The mean age of these patients was 41.22 days [Table 1].

All the patients in both the groups had antenatal and post-natal US, VCUG, and cystoscopy for the diagnosis of PUV [Table 2].

Among the 23 patients who had undergone circumcision at the time of valve ablation, nine (39.13%) had undergone urinary diversion for various reasons. One patient had high diversion and the rest had vesicostomy. Correspondingly, the number of patients who had undergone urinary diversion in the other group was 6 (40%). Valve ablation was done about 4–6 weeks later after the patients became hemodynamically and biochemically stable [Table 3].

On the mean followup period of 1 year only one patient (4.35%) in the circumcised group had suffered from Urinary tract infection after posterior urethral valve ablation.

The number of patients suffering from UTI after PUV ablation with 1 year follow-up had two episodes of UTI, whereas three patients (20%) who had not undergone circumcision had five episodes [Table 4].

Table 3: Mode of treatment in a patient with PUV

Group of patients	Primary	After diversion	
Number of PUV patients with circumcision	14	(After vesicostomy) 8	(After ureterostomy) 1
Number of PUV patients without circumcision	9	5	1

PUV: Posterior urethral valve

Table 4: Number of patients suffering from UTI after PUV ablation with 1 year follow up

No of patients with and without circumcision	Number of patients	Number of episodes
With circumcision	1	2
Without circumcision	3	5

PUV: Posterior urethral valve, UTI: Urinary tract infection

DISCUSSION

Boys with PUVs are at increased risk of suffering from febrile UTI apart from bladder dysfunction and renal damage.[3] Several studies had shown that circumcision reduces the risk of UTI[5] but there is a scarcity of data regarding the effect of circumcision in PUV patients.

Circumcision is an age-old surgery and is the most common surgical procedure carried out on pediatric population.[6] It is well accepted now that circumcision confers several benefits such as reduced incidence of UTI, sexual transmitted diseases, penile malignancy, acquired phimosis, paraphimosis, and a reduction in the occurrence of human papillomavirus related cervical cancer in female sexual partners. The reduction of zipper injury of the prepuceal skin is also a known benefit of circumcision. A meta-analysis by Greval *et al*.[5] has concluded that circumcision reduces the risk of UTI. They have stated that for a given risk of UTI in normal boys of about 1%, the number of boys needed to be treated to prevent one UTI is three. This figure goes down to 1–2 and 1–4 in 10% and 30% approximately for boys with recurrent UTI and high grade (>3) reflux, respectively. Hemorrhage and infection are the most common complication of circumcision, occurring at a rate of about 2%–10%. They concluded that the net clinical benefits are likely only in boys who are at high risk of UTI. Hence, their study thus indirectly supports the hypothesis of practicing circumcision in PUV patients.

Mukherjee *et al*., in their study, identified 78 patients who experienced severy eight episodes of UTI in an uncircumcised state. Twenty-seven of them were subsequently circumcised and they experienced only eight episodes of UTIs. Eighteen boys were diverted. The authors concluded that in PUV patients, circumcision reduces the incidence of UTI by 83% and that every circumcision prevents one UTI on an average.[3] Our results also match with this large series, i.e., 1/23 (4.35%) patients who underwent circumcision had two episodes of UTI whereas 3/15 (20%) uncircumcised patients had five episodes of UTI.

CONCLUSION

Circumcision following PUV ablation does confer protection from recurrent UTI and thus is helpful in delaying the ongoing renal damage. However, larger randomized control trial should be considered to validate our contentions.

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Original Article

Prevalence of Vitamin D Deficiency and its Effect on the Glycemic Control and Lipid Profile among Type 2 Diabetes Mellitus Patients in a Tertiary Care Hospital

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Abstract

Objective: The objective of the study was to find out the prevalence of Vitamin D deficiency among patients with type II diabetes mellitus (DM) and to assess the effect of Vitamin D in the control of blood sugar and lipid profile among patients with type 2 DM.

Material and Methods: Study setting: This study was conducted at diabetic clinic, Chennai Medical College Hospital and Research Centre, Irungalur, Tiruchirappalli. Study design: The present study was a hospital-based analytical cross-sectional design. Sample size: The sample size was taken as 90 (using the formula $4pq/l^2$). Analysis: The data collected were entered and analyzed using the SPSS software package (Version 21). Descriptive statistics (mean, standard deviation and 95% confidence interval) and appropriate tests of significance (ANOVA) were applied to establish the relationship between the study variables. $P < 0.05$ was considered to be statistically significant.

Results: We found that there was a significant reduction in all the glycemic indicators over the progressive weeks among the group of participants receiving Vitamin D supplements. We have also reported a uniform reduction in all the lipid profile values and glycemic indicators across all the three groups in the progressive weeks, with a significant reduction in the group receiving Vitamin D supplements.

Conclusions: Vitamin D supplementation improves glycemic control and can reduce or prevent the development of insulin resistance in type 2 diabetes mellitus patients. Considering the multitude of diseases associated with Vitamin D deficiency, increasing the population's awareness of the beneficial effect of Vitamin D on health will be an important strategy overall.

Key words: Vitamin D, Type 2 diabetes mellitus, Glycemic control, Lipid profile

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia as a result altered carbohydrate, fat, and protein metabolism. Type 2 DM counts the remaining 90–95% of world diabetic population. The World Health Organization estimated in 2000, 171 million people were suffered from this disease and this number is believed to double by the year 2030.[1]

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Vitamin D deficiency is believed to affect not only skeletal but also extra skeletal organs leading to various diseases. Vitamin D deficiency has been found to be associated with increasing incidence of chronic illnesses such as DM, cardiovascular diseases, and malignancies.[2,3] The role of Vitamin D in glycemic control and lipid profile has a mixed documentation, while studies suggest that elevated Vitamin D levels are associated with improved glycemic control in type 2 DM (T2DM),[4] some studies have observed no such effect.[5] The effect of Vitamin D on serum lipids in T2DM is not exactly known.[6] Studies have also documented an inverse relationship between triglycerides, total cholesterol level Vitamin D.[7]

Vitamin D deficiency is prevalent all over the world, though Vitamin D can be synthesized in the skin by exposure to sunlight, this source alone is not enough. Vitamin D

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deficiency is the most left as an un-treated nutritional deficiency.[8] It affects people regardless of their age, sex, ethnicity, and topography. The dietary sources rich in Vitamin D are not affordable to most of the Indian population. Vitamin D supplements though available in the market are not consumed regularly due to their cost and decreased awareness regarding the supplements.[2] The present study was undertaken to assess the effect of Vitamin D in the control of blood sugar and lipid profile in the patients with T2DM.

MATERIALS AND METHODS

Study Setting

The study was conducted at the diabetic clinic, Chennai Medical College Hospital and Research Centre, Irungalur, Tiruchirappalli.

Study Design

The present study was a hospital-based analytical cross-sectional design.

Study Population

The participants included in the study were 36–60-year-old adults from both genders who had been previously diagnosed with T2DM and were all under treatment with metformin treatment.

Sample Size

The prevalence of T2DM is rural Tamil Nadu[9] 6% and, absolute error in estimated prevalence-5%, the sample size was taken as 90 (using the formula $4pq/l^2$).

Ethical Clearance

The study was approved by the Institutional Ethical Committee, Research Cell of Chennai Medical College Hospital and Research Centre.

Data Collection Tool

Data collection was done during working hours at a time feasible to the respondents. The study was conducted in the hospital premises after obtaining prior permissions from the concerned authorities. After obtaining informed consent from the participants, they were divided into three groups, based on their treatment schedules and observed. The first group consisted of T2DM on metformin therapy + normal serum vitamin 25(OH)D level and the second group included T2DM on metformin therapy + decreased serum 25(OH)D level and in the third group, T2DM on metformin therapy + decreased serum 25(OH)D level + Cholecalciferol 60000 IU weekly. The respondents were asked to fill a questionnaire which covered information on socio-demographic data. Biochemical parameters were measured by drawing 5 ml venous blood, the samples were collected from the subjects in all the three groups on 0^{th} day at the end of 4^{th}, 8^{th}, and 12^{th} weeks of the study period.

Statistical Analysis

The data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) (version 21.0) software package. Descriptive statistics were used to define the study population. Categorical and ordinal variables were expressed as frequency/percentages. Continuous variables were expressed as mean and standard deviation. Appropriate tests of significance (ANOVA) were applied to the study variables to establish the relationship between the study variables. $P < 0.05$ was considered to be statistically significant.

RESULTS

Majority of the sample population, 37 (41.1%) respondents were in the age group of 50–59 years. The mean age group of the respondents was 49.5 ± 7.44. Among the study participants, more than half were male 54 (60%) [Table 1].

Comparison of Mean Glycemic Values [Table 2]

Our results showed that among the study participants the mean fasting blood sugar for the first group (T2DM on metformin therapy + normal serum vitamin 25(OH)D level) at 0, 4, 8, and 12 weeks were 119.9 ± 8.4, 117.4 ± 7.4, 148.5± 5.4, and 112.5 ± 6.3, respectively. While in the second group (T2DM on metformin therapy + decreased serum 25(OH)D level), the values were 137.3 ± 6.2, 136.0 ± 7.1, 134.1 ± 4.2, and 131.9 ± 6.2. In the third group (T2DM on metformin therapy + decreased serum 25(OH) D level + Cholecalciferol 60000 IU weekly), the results were 139.2 ± 6.4, 134.9 ± 6.42, 130.7 ± 6.52, and 124.9 ± 8.07. We found that the reduction in fasting blood sugar was significantly more ($P = 0.032$) in the group receiving Vitamin D supplements [Table 2].

Table 1: Socio-demographic characteristics of the respondents (*n*=90)

Variable	Frequency (%)
Age	Mean age of respondents 49.5±7.44
30–39	14 (15.5)
40–49	32 (35.5)
50–59	37 (41.1)
>60	7 (7.9)
Gender	
Male	62 (68.8)
Female	38 (31.2)
Religion	
Hindu	76 (84.4)
Muslim	4 (4.5)
Christian	10 (11.1)
Marital status	
Single	7 (6.3)
Married	83 (93.7)

Table 2: Distribution and comparison of mean glycemic values among the respondents (*n*=90)

Variable	Group I	Group II	Group III	Test of significance* (ANOVA)
Fasting blood sugar (weeks)				
0	119.9±8.4	137.3±6.2	139.2±6.4	*P*=0.032
4	117.4±7.4	136.0±7.1	134.9±6.42	
8	148.5±5.4	134.1±4.2	130.7±6.52	
12	112.5±6.3	131.9±6.2	124.9±8.07	
Postprandial blood sugar				
0	159.9±7.4	177.6±6.7	177.9±8.2	*P*=0.024
4	157.5±5.3	177±6.8	175.0±6.8	
8	154.6±6.6	174.6±5.4	170.7±6.6	
12	147.7±4.4	171.8±4.8	163.6±10.7	
Insulin resistance levels				
0	2.19±0.6	3.49±0.3	3.6±0.5	*P*=0.037
4	2.1±0.2	3.4±0.3	3.3±0.5	
8	1.95±0.2	3.22±0.2	2.9±0.4	
12	1.83±0.3	3.1±0.3	2.6±0.4	
HbA_1c levels				
0	6.44±0.4	7.36±0.4	7.46±0.31	*P*=0.046
4	6.35±0.5	7.27±0.3	7.24±0.32	
8	6.21±0.3	7.17±0.5	7.03±0.32	
12	6.15±0.2	6.81±0.3	6.77±0.32	

*$P<0.05$ was taken to be statistically significant. HbA_1c: Hemoglobin A1c

The postprandial blood sugar values for the first group at 0, 4, 8, and 12 weeks were 159.9 ± 7.4, 157.5 ± 5.3, 154.6 ± 6.6, and 147.7 ± 4.4, respectively, while in the second group, the values were 177.6 ± 6.7, 177 ± 6.8, 174.6 ± 5.4, and 171.8 ± 4.8, respectively. In the third group, the results were 177.9 ± 8.2, 175.0 ± 6.8, 170.7 ± 6.6, and 163.6 ± 10.7. We found that the reduction in postprandial blood sugar was significantly more (P =0.024) in the group receiving Vitamin D supplements.

The insulin resistance levels for the first group at 0, 4, 8, and 12 weeks were 2.19 ± 0.6, 2.1 ± 0.2, 1.95 ± 0.2, and 1.83 ± 0.3, respectively, while in the second group, the values were 3.49 ± 0.3, 3.4 ± 0.3, 3.22 ± 0.2, and 3.1 ± 0.3, respectively. In the third group, the results were 3.6 ± 0.5, 3.3 ± 0.5, 2.9 ± 0.4, and 2.6 ± 0.4, respectively. We found that there was a significant reduction in insulin resistance levels (P = 0.037) in the group receiving Vitamin D supplements.

The HbA1C levels for the first group at 0, 4, 8, and 12 weeks were 6.44 ± 0.4, 6.35 ± 0.5, 6.21 ± 0.3, and 6.15 ± 0.2, respectively, while in the second group, the values were 7.36 ± 0.4, 7.27 ± 0.3, 7.17 ± 0.5, and 6.81 ± 0.3, respectively. In the third group, the results were 7.46 ± 0.31, 7.24 ± 0.32, 7.03 ± 0.32, and 6.77 ± 0.32, respectively. We found that there was a significant reduction in HbA1C levels (P = 0.029) in the group receiving Vitamin D supplements.

Comparison of Mean Lipid Profile Values

Our results showed a uniform reduction in all the lipid profile values across all the three groups in the progressive weeks, except for high-density lipoproteins (HDLs) which showed a significant increase. There was a significant reduction in triglyceride (TGL) levels in all three groups in the progressive weeks. The Vitamin D levels were also significantly higher in the third group, as shown in Table 3.

Weekly Comparison of Vitamin D Levels in Group Receiving Supplements

In the group receiving Vitamin D supplements, we found that there was a significant reduction in all the glycemic indicators over the progressive weeks, as shown in Table 4. We also noted that with regular Supplementation of vitamin D there was a significant reduction in the lipid profile values [Table 4].

DISCUSSION

The increased prevalence of DM is attributed to low serum Vitamin D status.[10] Vitamin D supplementation to T2DM patients increases serurm 25(OH)D level.[11] Studies in humans have shown that Vitamin D supplementation in infancy reduces the risk of type 1 DM during early adulthood. As Vitamin D modulates insulin receptor (INS-R) gene expression and insulin secretion, Vitamin D deficiency is an environmental etiological factor for T2DM.

Vitamin D supplementation significantly reduces fasting blood glucose, postprandial blood glucose, and HbA1c levels ($P < 0.05$) in Group III T2DM patients. Further, an inverse relationship between serum 25(OH) D and HbA1c level was observed.[12] Vitamin D exerts this

Table 3: Distribution and comparison of mean lipid profile values and Vitamin D values among the respondents (*n*=90)

Variable	Group I	Group II	Group III	Test of significance* (ANOVA)
Total cholesterol levels (weeks)				
0	192.4±7.3	194.9±8.1	196.03±7.1	*P*=0.14
4	191.2±5.6	194.1±6.2	191.64±9.9	
8	189.9±8.4	193.3±7.8	188.58±7.7	
12	189±6.8	192.6±5.7	185.30±6.4	
TGL levels (weeks)				
0	234.7±8.3	238.7±7.8	238.6±9.6	*P*=0.045
4	233.3±6.9	238.09±6.5	235.1±9.9	
8	231.8±5.6	237.6±5.2	227.25±7.7	
12	230.5±7.4	236.7±8.3	226.01±6.7	
LDL levels (weeks)				
0	104.6±5.9	109.9±6.1	114.2±5.3	*P*=0.98
4	103.5±7.4	111.9±8.3	111.03±4.7	
8	102.5±6.2	109.4±5.4	109.4±5.5	
12	101.5±8.1	108.5±7.8	109.8±11.4	
HDL levels (weeks)				
0	40±2.1	38.5±7.3	38.5±2.1	*P*=0.046
4	40.7±1.7	39.1±6.8	40.1±1.4	
8	41.5±3.4	39.7±8.5	39.9±6.8	
12	42±1.6	40.3±5.6	42.2±2.0	
Vitamin D levels (weeks)				
0	30.9±6.2	14.33±6.3	12.8±4.1	*P*=0.037
4	31.3±7.8	14.88±8.4	17±6.0	
8	31.9±5.7	16.05±5.8	21.9±7.1	
12	32.4±8.5	17.13±7.6	28.1±7.6	

*$P<0.05$ was taken to be statistically significant. TGL: Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Table 4: Effect of Vitamin D levels on glycemic indicators and lipid profile values among the respondents (Group III) receiving Vitamin D therapeutic supplements (*n*=30)

Variable	0 weeks	4 weeks	8 weeks	12 weeks	Test of significance* (ANOVA)
	Mean±SD (CI)				
Fasting blood sugar	139.2±6.4 (136.8–141.6)	134.9±6.42 (132.5–137.3)	130.7±6.52 (128.2–133.1)	124.9±8.07 (121.8–127.9)	0.017
Postprandial blood sugar	177.9±8.2 (174.8–181)	175.0±6.8 (172.5–177)	170.7±6.6 (168.2–173.1)	163.6±10.7 (159.6–167.9)	0.009
Insulin resistance levels	3.6±0.5 (3.4–3.8)	3.3±0.5 (3.1–3.4)	2.9±0.4 (2.8–3.1)	2.6±0.4 (2.4–2.8)	0.025
HbA_1c levels	7.4±0.31 (7.34–7.57)	7.2±0.32 (7.12–7.36)	7.0±0.32 (6.9–7.15)	6.7±0.32 (6.6–6.8)	0.029
Total cholesterol levels	196.0±7.1 (193.3–198.5)	191.6±9.9 (188.9–194.3)	188.5±7.7 (185.7–191.4)	185.3±6.7 (182.7–187.8)	0.041
TGL levels	238.6±9.6 (234.9–242.2)	235.1±9.9 (231.4–238.8)	227.6±12.3 (222.6–231.8)	226.0±11.2 (221.8–230.2)	0.033
LDL levels	114.2±5.3 (112–116)	111.0±4.7 (109–112)	109.4±5.5 (107–111)	109.8±11.4 (105–114)	0.09
HDL levels	38.5±2.1 (37.7–39)	40.0±1.4 (39.5–40.5)	39.9±6.8 (37.3–42.4)	42.2±2.0 (41.5–43)	0.07
Vitamin D levels	12.8±4.1 (11.3–14.4)	17.0±6.0 (14.7–19.3)	21.9±7.1 (19.2–24.5)	28.1±7.6 (25.2–30.9)	0.016

*$P<0.05$ was taken to be statistically significant. CI: Confidence interval, TGL: Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SD: Standard deviation, HbA_1c: Hemoglobin A1c

beneficial effect by direct and indirect mechanisms. Vitamin D promotes pancreatic β-cell function and increases insulin secretion in numerous ways.[13] The presence of Vitamin D receptors (VDR) and binding of

25(OH) D with Vitamin D binding proteins in β cells of pancreas[12] leads to the transcription of genes regulated by 25(OH)D and facilitates the secretion of insulin from pancreatic β cells activation of Vitamin D occurs in pancreatic β-cells by intracellular 1-α-hydroxylase enzyme.[13] Vitamin D, by its direct action, enhances insulin secretion by forming $1,25(OH)_2D_3$-RXR-VDR complex, which binds to Vitamin D responsive elements found in the insulin gene promoter region, enhancing the transcriptional activation of the insulin gene, and increase insulin synthesis.[14] Insulin secretion is a calcium-dependent process and is influenced by calcium influx through the cell membrane.

Vitamin D indirectly promotes calcium influx into the β-cells of the pancreas by regulating calbindin, a cytosolic calcium-binding protein found in β-cells resulting in increased insulin synthesis.[15] Vitamin D supplementation along with metformin in Group III T2DM patients also significantly reduces insulin resistance as compared to Group II T2DM patients with metformin monotherapy. The mechanism by which Vitamin D reduces insulin resistance is a complex one. Vitamin D enhances insulin sensitivity by stimulating the transcription of INS-R gene[14] and thereby reduces insulin resistance.[16] Further Vitamin D exerts anti-apoptotic effect by attenuating the expression of pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, tumor necrosis factor-alpha, and nuclear factor kappa-beta involved in insulin resistance Vitamin D also suppresses the renin gene reducing hyperglycemic induced increase in renin levels in pancreatic β cells and blockade of renin-angiotensin activity. This has been proposed as a novel target for the management of diabetes and metabolic syndrome.[17]

Regarding the analysis of the lipid profile, *post hoc* test reveals a significant reduction in TGL level in Group III T2DM patients as compared to Group II T2DM subjects. Vitamin D also reduces total cholesterol levels and increases HDL levels but insignificantly. Vitamin D exerts its action on lipid metabolism by activating transcriptional factor, peroxisome proliferator-activated receptor-δ. It is implicated in the regulation of fatty acid metabolism in skeletal muscles and adipose tissue.[18,19] The inhibitory effect of Vitamin D on lipids facilitates a reduction in insulin resistance.

The highlight of the present study is the identification of a higher prevalence of Vitamin D deficiency and insufficiency among T2DM study population. Vitamin D supplementation significantly increases serum 25(OH)D level in Group III T2DM subjects.

CONCLUSIONS AND RECOMMENDATIONS

Vitamin D improves glycemic control in T2DM patients by lowering fasting blood glucose and HbA1c levels. An inverse relationship between serum 25(OH)D and HbA1c levels in T2DM patients has been observed. Vitamin D also reduces TGL level and improves HDL level in T2DM patients. Further, Vitamin D promotes insulin synthesis and improves insulin sensitivity in T2DM patients. Hence, Vitamin D supplementation improves glycemic control and can reduce or prevent the development of insulin resistance in T2DM patients. Considering the multitude of diseases associated with Vitamin D deficiency, increasing the population's awareness of the beneficial effect of Vitamin D on health will be an important strategy overall.

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Original Article

Assessment of Nutritional Status of Sputum Positive Pulmonary Tuberculosis Patients in a Medical College

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Abstract

Introduction: Tuberculosis (TB) has been understood as a disease of wasting since it causes significant deficiencies in nearly every nutritional marker.

Aims and Objective: The purpose of this study is to assess the nutritional status of patients of sputum positive pulmonary TB patients and to identify the factors if malnutrition is present.

Materials and Methods: Two hundred patients of sputum positive for pulmonary TB were selected in a medical college on an outpatient service basis. The most common nutritional and biochemical assessment was done by blood hemoglobin and serum albumin level. All other relevant parameters were also recorded.

Results: About 10.5% of patients of severe anemia, 20% of patients of moderate anemia, and 35.5% of patients of mild anemia were found. About 12.5% cases of severe albumin deficiency (<2 g/dl), 24.5% cases of moderate albumin deficiency (≤2.5 g/dl), and 37% cases of mild albumin deficiency (≤3 g/dl) were also noted. There was a significant correlation between decrease calorie intake and decrease albumin levels. In the rural population, there were 79.16% malnourished in <20 years age group. Male preponderance (66%) was noted with male:female ratio of 2:1. About 86.5% of the patients were illiterate. About 87% of patients belong to lower social class. About 37% of cases were smoker and out of these smokers, 71% were malnourished. About 35% of cases were alcoholic and out of these alcoholic, 71% were malnourished.

Conclusion: Sputum positive TB patients have poor nutritional status. Malnutrition is found in individuals with factors of rural background, male patients, poor literary status, low family income, smoking, and alcohol addiction.

Key words: Albumin, Hemoglobin, Malnutrition, Tuberculosis

INTRODUCTION

Tuberculosis (TB) is a contagious disease which is closely related to poverty, under-nutrition, and poor immune function.[1] Body mass index (BMI) (kg/m^2), skinfold thickness, mid-upper arm circumference, grip strength, body fat percentage, calorie stores, muscle mass, serum albumin, blood hemoglobin, plasma retinol, plasma zinc, selenium, iron, and Vitamins A, C, D, and E have all been found to be depressed in TB patients.[2-4] Several vitamin deficiencies have been seen to be common in TB patients. Furthermore, the risk of active TB has also been ascribed to vitamin deficiency.[5] Therefore, it can be difficult to distinguish vitamin deficiency that happened from the disease from vitamin deficiency that predisposed to the development of the disease.[6,7] Vitamin A deficiency is perhaps the best-studied micronutrient deficiency in TB with many studies demonstrating markedly decreased serum levels in TB patients.[8-10] In TB, weight loss is one of the most common manifestations of nutritional wasting, though probably not the most clinically significant in terms of effect on health and survival. The bulk of weight loss in patients with TB is fat mass, though the fat-free component

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also lost in significant amounts, has more of a result on the physical functioning of the patient. Protein deficiency has been described in TB and albumin and prealbumin have been found to be useful markers both for the diagnosis of deficiency and monitoring of its reversal.[11,12] Like TB, HIV often results nutritional deficiencies and clinical wasting, particularly in the later stages.[13,14] Malnutrition decreases the efficacy of the Bacillus Calmette–Guérin (BCG) vaccine in two different ways. First, the maintenance of good nutrition is important for continuing vaccine-induced immune protection. Due to deteriorating nutritional status, tuberculin skin test and BCG vaccination result in a marked decrease in the size of indurations.[15] Second, severe malnutrition during BCG administration can permanently affect vaccine-induced immune protection.[16]

Review of Literature

TB is associated with various socio-economic factors such as poverty, poor housing, and economic deprivation, which causes poor nutritional status and poor immune function. Nutrition is important for making healthy and proper functioning of all systems of the body including the immune system. This is because malnutrition weakens the immune system and thus the capability of the individual to fight fatal infection like TB and their ability to halt disease progression will be compromised.[17] Treating of comorbid conditions has value for improving access and responses to TB treatment and it should be a part of care for people with TB. The aim should be to improve the general health and quality of life. The food and nutritional care successfully result health promotion and disease prevention. Under-nutrition is an important risk factor as well as a common consequence of TB. However, nutrition assessment and care are important components of improving rehabilitation and quality of people's life. Improved nutritional care and support can improve the health outcomes for people with TB. To improve the clinical care of people with TB, the focus is specially done on nutritional assessment, counseling, and management.[18]

Malnutrition refers to either overnutrition or undernutrition or both. Undernutrition refers to the nutritional status of the person having suboptimal and thereby health and growth will be impaired. Undernutrition may be due to illness-causing decreased nutrient intake and metabolism or result from inadequate intake of macronutrients, micronutrients, or both.[19-21] Undernutrition is commonly associated with malabsorption, pneumonia, TB, and HIV. The association between TB and undernutrition has been known since before. Undernutrition is endemic in India. About 34% of men and 36% of women 15–49 years in India are undernourished as per NFHS-3 estimates. As undernutrition, the leading cause of immunodeficiency globally, weakens power to fight against the TB. These people are at risk up to 4 times more likely to develop TB disease than healthy people.[22] TB makes undernutrition worse and undernutrition weakens the immunity power. As a result, latent TB will develop into active disease.[23] Most patients of active TB are in a catabolic state and result in weight loss.[24-26]

Weight loss is found to be one of the most common presenting complaints of patients with TB.[27,28] Weight loss in TB can be caused by several factors such as reduced food intake due to loss of appetite, nausea and abdominal pain, nutrient losses from vomiting and diarrhea, and metabolic changes due to the disease.[29,30] Low BMI and lack of adequate weight gain with TB treatment are the increased risk factors for death[31] and TB relapse[32,33] and may indicate the severity of TB, poor treatment response and/or the presence of other comorbid conditions.

TB can worsen preexisting undernutrition by decreasing appetite and by increased catabolism. High prevalence of undernutrition in TB patients results in increased deaths and risk of relapse. The prevalence, severity, and implications of undernutrition in Indian TB patients particularly are found from India's rural areas compared to urban areas.[34]

Nutrition care or management of persons with active TB with moderate undernutrition includes assessing their nutritional status, identifying, and treating the underlying causes of malnutrition and improving the nutrient intake through education, counseling, food assistance, and other activities.[35] TB is commonly associated with comorbidities such as HIV, diabetes mellitus, smoking, and alcohol or substance misuse. These should be fully considered during nutrition screening, assessment, and counseling. Unintentional weight loss is one of the best predictors of worst clinical outcome. In older people, it is associated with significant morbidity and mortality.[36]

Aims and Objectives

Main aims and objectives of this study are as follows:

1. To assess the nutritional status of the patient having sputum positive pulmonary TB
2. If malnutrition is found, assessment of the factors affecting malnutrition.

MATERIALS AND METHODS

The study was conducted from December 15, 2015, to September 15, 2016, in a government medical college. It was a cross-sectional study of sputum smear-positive TB patients. As per the previous year data of sample collection (2014), on an average 1482 sputum smear-positive patients were diagnosed and treated in outpatient

department, roughly seven sputum smear-positive patients were diagnosed per day. Hence, every seventh patient who was diagnosed as sputum smear-positive in outpatient department by systematic random sampling technique was opted for the study. The desired sample size of 200 was achieved in almost 10 months. Anthropometric measurements were done using parameters such as height, weight, and BMI. The Quetelet index relates weight (kg) to the square of the height (m^2), which enables calculation of BMI. The WHO categorizes underweight as BMI <18.5, normal as 18.5–24.9, overweight as 25–29.9, and obese as 30–39.9, and extreme obesity >40. Most common nutritional and biochemical assessment was done by blood hemoglobin and serum albumin level.

Inclusion Criteria

All sputum positive patients diagnosed as TB as per diagnostic algorithm under RNTCP by sputum microscopy having consent for study had been included in the study.

Exclusion Criteria

The following criteria were excluded in the study:

1. Patient refusing to give consent to participate in the study
2. Sputum negative pulmonary TB
3. Extrapulmonary TB
4. Carcinoma lung
5. Other causes of pulmonary diseases.

The pre-tested, semi-structured, and validated questionnaire was used to get the information about the personal history, socio-economic status, nutritional history, and physical examination. The questionnaire included the personal history of the patient, i.e., name, age, sex, address, education, occupation, and income. Modified Kuppuswamy scale was used to assess socio-economic status of the patients which is based on three parameters that are education, occupation, and income.

Furthermore, medical history of the patient regarding RNTCP ATT category of the patient, HIV status, and metabolic disease was enquired. History of smoking and alcoholism was taken. Patients were also examined physically for vital signs, pallor etc. Patient was investigated for anemia and hypoproteinemia. Nutritional history including daily diet, calorie calculation on diet basis, and calorie requirement according to weight and occupation was taken and assessed.

BMI was calculated by Quetelet's index (Weight in kg/height in m^2). Historically, serum proteins such as albumin have been widely used by physicians to determine patient nutritional status. Serum albumin <2 g/dl is defined as severe, <2.5 g/dl is moderate, and <3 g/dl is mild malnutrition.

History of weight loss and signs of undernutrition, such as visible wasting or edema, were noted. Clinical assessment for comorbid conditions and concurrent treatments was also recorded. History and clinical diagnosis, medical history was helpful in raising suspicion for increased risk of malnutrition and the presence or absence of inflammation. Physical examination revealed the presence of several of the diagnostic characteristics of malnutrition such as weight loss or gain, fluid retention, loss of muscle or fat, and other signs of specific macro and/or micronutrient deficiencies.

Screening included the questions regarding loss of appetite, loss of weight, mobility, any stress, and BMI. Scoring was done after this. Then, assessment was done by asking about the diet including meals, protein intake, fluid intake, and nutritional status. Mid arm circumference was measured by measuring the circumference of the left upper arm, measured at the mid-point between the tip of the shoulder and the tip of the elbow. Calf circumference was measured at the fullest part of the calf. Screening and assessment score was calculated. Information regarding food and nutrient intake were obtained from the patient and/or caregiver. A modified diet history, 24 h recall, "calorie counts" (either observed intake/estimated post-meal plate waste), and/or prior documentation of periods of inadequate food intake in the patient's medical record were used as "evidence" of inadequate intake. A food frequency multi-question questionnaire was used to explore dietary intake over a period of time.

OBSERVATION AND RESULTS

The present study was conducted on 200 cases of sputum positive pulmonary TB patients.

Following observations were drawn from the results of present study:

1. Out of 200 cases maximum number of patients were from 41 to 60 years age group (35.5%), followed by 21–40 years' age group (30.5%)
2. Mean age was 45.36 ± 18.974
3. In rural population, there were 79.16% malnourished in <20 age group
4. About 63.93% were malnourished in 21–40 age groups, of which 64.1% were from rural area. About 54.92% were malnourished in 41–60 age groups, of which 74.35% were from rural area. About 59.09% were malnourished in more than 60 age groups. Among these, 84.61% from rural area [Table 1]
5. Most of the patients were from rural areas, i.e., 70.5% cases whereas urban area patients were 29.5%
6. Male preponderance (66%) was noted in our study, with male:female ratio 2:1

7. Out of 141 rural patients, 68.08% were males and 31.91% were females
8. Out of 59 urban patients, 61.01% were males and 38.98% were females
9. As per the modified Kuppuswamy classification, most of our patients (86.5%) were illiterate or studied up to primary school level whereas only 2% were graduates [Table 2]
10. Most of (85.5%) our patients were unemployed (41%) and unskilled worker (44.5%), whereas only 1.5% was skilled worker in regular employment
11. On the basis of education, occupation, and income, most of our patients belong to lower (87%) Kuppuswamy social class, of which 84.5% were in upper lower class and 2.5% in lower class, followed by middle Kuppuswamy social class (13%), of which 11% were in lower-middle, and 2% were in upper-middle class [Table 3]
12. Diabetes mellitus was present in 25.5% of cases
13. History of contact with active TB case was present in 8.5% of cases
14. About 37% of cases were smoker and out of these smokers, 71% were malnourished [Table 4]
15. About 35% of cases were alcoholic and out of these alcoholic, 71% were malnourished [Table 4]
16. Weight loss was reported by 95.5% cases, of which 75% reported more than 3 kg loss and 2.5% having 1–3 kg loss in past 1 week
17. Pallor was present in 85% of cases. Out of these, 65.29% were malnourished [Table 5]
18. Pallor with malnourished was seen in 69.36% of rural patients and 30.63% urban patients. Edema was present in 62.5% of cases
19. 61.5% cases have BMI below normal range as per the WHO criteria, i.e., underweight (<18.5). Mean BMI was 17.50 ± 3.94 [Table 6]
20. Out of 61.5% underweight patients, 29.26% were from urban area, of which 58.33% were males and 41.67% were females. About 70.73% were from rural area, of which 66.67% were males and 33.33% were females [Table 7]
21. Patient reported MIS questionnaire after taking history and doing examination. About 79% of cases were classified as malnourished category
22. Mid arm circumference was <21 cm in 76% of cases, and calf circumference was below 31 cm in 72% of cases
23. About 12.5% cases were having severe albumin deficiency (<2 g/dl), 24.5% were having moderate

Table 1: Distribution of patients according to the age

Age group (years)	≤20	21–40	41–60	>60
Number of patients (%)	24 (12)	61 (30.5)	71 (35.5)	44 (22)
Malnourished (%)	19 (79.16)	39 (63.93)	39 (54.92)	26 (59.09)
Rural (%)	11 (57.89)	25 (64.1)	29 (74.35)	22 (84.61)
Urban (%)	8 (42.11)	14 (73.68)	10 (52.63)	4 (21.05)
Mean±SD (years)	45.36±18.974			

Table 2: Distribution of patients as per literacy level

Education	Number of patients (%)
Primary school certificate, illiterate	173 (86.5)
Intermediate, post-high school diploma, high school certificate	23 (11.5)
Graduate or postgraduate	4 (2.0)
Total	200 (100.0)

Table 3: Distribution of patients according to the modified Kuppuswamy scale

Socioeconomic status	Number of patients (%)
Lower	5 (2.5)
Upper lower	169 (84.5)
Lower middle	22 (11.0)
Upper middle	4 (2.0)
Total	200 (100.0)

Table 4: Distribution of patients based on their addiction

Addiction	Number of patients (%)	Malnourished (%)
Smoking	74 (37.0)	53 (71)
Alcoholism	70 (35.0)	50 (71)

Table 5: Distribution of pallor in patients

Pallor	Number of patients (%)	Malnourished (%)
Yes	170 (85.0)	111 (65.29)
No	30 (15.0)	-
Total	200 (100.0)	-

Table 6: Distribution of patients in relation to body mass index (who classification)

BMI grading	Number of patients (%)
Overweight (>25)	6 (3)
Normal (18.5–24.9)	71 (35.5)
Underweight (<18.5)	123 (61.5)
Total	200 (100.0)
Mean±SD	17.50±3.94

BMI: Body mass index, SD: Standard deviation

Table 7: Distribution of underweight patients in relation to area and gender

Underweight	Number of patients (%)	
	Male	Female
Rural	58 (66.67)	29 (33.33)
Urban	21 (58.33)	15 (41.67)

Table 8: Correlation between differential serum protein-albumin and calorie intake

Differential Serum Protein-albumin	Calorie intake, *n* (%)				Total
	1%–25%	26%–50%	51%–75%	76%–100%	
<2 (g/dL)	3 (12.0)	13 (52.0)	9 (36.0)	0 (0.0)	25 (100.0)
≤2.5 (g/dL)	4 (8.2)	31 (63.3)	12 (24.5)	2 (4.1)	49 (100.0)
≤3 (g/dL)	5 (6.8)	31 (41.9)	29 (39.2)	9 (12.2)	74 (100.0)
>3 (g/dL)	11 (21.2)	20 (38.5)	14 (26.9)	7 (13.5)	52 (100.0)
P			0.031		
Significance			Significant		

Table 9: Distribution of hemoglobin level of patients (who classification)

Hemoglobin in (g/dL)	Number of patients (%)
<7 (severe)	21 (10.5)
7–8.9 (moderate)	40 (20)
9–10.9 (mild)	71 (35.5)
≥11 (normal)	68 (34)

albumin deficiency (≤2.5 g/dl), and 37% having mild albumin deficiency (≤3 g/dl). About 26% of patients have serum albumin in the normal range. There was a significant correlation between decrease calorie intake and decrease albumin in patients [Table 8]

24. About 10.5% of patients were having severe anemia. About 20% of patients were having moderate anemia. About 35.5% of patients were having mild anemia. About 34% had hemoglobin in normal range [Table 9].

Majority of the malnourished patients were from rural background. In contrast to normal population, higher proportion of malnourished was seen in males. Alcohol and smoking were found to be other factors affecting malnutrition. There is increased prevalence of malnutrition among the illiterate group. Poor nutrition status was seen in patients having low income.

DISCUSSION

TB is associated with poverty and malnutrition. Nutritional status is significantly lower in patients with active TB compared with healthy controls. Factors affecting malnutrition need to be identified so that these can be addressed to have impact on TB. In the present study, out of 200 cases, maximum number of patients was from 41 to 60 years of age group (35.5%), followed by 21–40 years of age group (30.5%). These age group individuals are mostly out of home for earning purpose. It indicates high burden in economically earning group and impacts on financial burden on society. About 22% were in the age group >60 years and 12% were in the age group <20 years. Mean age of patients is 45.36 ± 18.974. About 79.16% were malnourished in ≤20 age group, of which 57.89% were from rural areas. About 63.93% were malnourished in 21–40 age groups, of which 64.1% were from rural areas. About 54.92% were malnourished in 41–60 groups, of which 74.35% were from rural areas. Similarly, 59.09% were malnourished in >60 age group, of which 84.61% were from rural areas. In a study conducted by Nunez-Rocha *et al.*,[37] (2000), the mean age was 42.4 ± 19.9 years which was almost similar to present study. In the present study, significant male predominance was found with male:female 2:1. Males were 66% and females were 34%. Likely due to male dominating society, more males are taking healthcare services than females and as males are mostly out of their home for earning purpose, so more likely to come in contact with open cases of TB. In a study conducted by Dargie *et al.*,[17] around 55.8% were males and 44.2% were females which is similar to our study. In our study, as per modified Kuppuswamy classification, most of our patients (86.5%) were illiterate or studied up to primary school level whereas only 2% were graduate showing the importance of literacy as per Table 4. In a study conducted by Dargie *et al.*,[17] 50.3% were illiterate or studied up to primary school. About 18.3% were tertiary educated. Most of our patients in present study were from rural area and India is a developing country. Hence, illiteracy is a major problem.

In the present study, most of (85.5%) our patients were unemployed (41%) and unskilled worker (44.5%), whereas only 1.5% were skilled worker in regular employment as per Table 5. In a study conducted by Dargie *et al.*,[17] 28.3% were unemployed and 14.7% were daily laborers. About 23.1% were employed. This difference is due to different sample collection. India is a developing country where unemployment is a major problem. Hence, earning is also affecting as observed. Earning is also a factor contributing in cause of malnutrition. On the basis of education, occupation and income, most of our patients belong to lower (87%) socio-economic class, of which 84.5% were in upper lower class and 2.5% in lower class, followed by middle social class (13%), of which 11% were in lower-middle and 2% were in upper-middle class. In the present study, HIV positivity was seen in only 2.5% cases. In a study conducted by Manjareeka and Nanda,[38] 12.3% of TB patients were HIV positive. In a study conducted by Giri *et al.*,[39] 17% of patients were HIV positive. In the present

study, diabetes mellitus was present in 25.5% of cases. In a study conducted by Raghuraman *et al.*,[40] the prevalence of diabetes in TB patients was found to be 29% cases which is similar to the present study.

In the present study, 37% of cases were smoker. In a study conducted by Mahishale *et al.*,[41] 32.21% were smokers which was similar to our study. In a study by Wang and Shen,[42] the proportion of cigarette smoking was 54.6% in TB cases, which was significantly higher than in controls (45.1%) in China. No female was smoker in our study. In the present study, 35% of cases were alcoholic. No females consumed alcohol. In a study conducted by Suhadev *et al.*,[43] 29% were found to consume alcohol which was very similar to our study.

Patient reported MIS questionnaire after taking history and doing an examination. Seven-nine percent of cases were classified as malnourished category, 17% were at risk of malnutrition, and 4% cases were in normal range. In the present study, 61.5% of cases had BMI below normal range as per the WHO classification and the mean BMI was 17.50 ± 3.94. Out of 123 underweight patients, 29.26% were from urban area and 70.73% were from rural areas. About 58.33% were males and 41.67% were females from urban areas. About 66.67% were males and 33.33% were females from rural areas. In a study conducted by Nunez-Rocha *et al.*,[37] mean BMI was 19.8 ± 3.2; 57% presented malnutrition. In a study conducted by Kumar *et al.*,[44] mean BMI was 17.33 which was same as our study. About 12.5% cases were having severe albumin deficiency (<2 g/dl), 24.5% were having moderate albumin deficiency (≤2.5 g/dl), and 37% having mild albumin deficiency (≤3 g/dl). About 26% patients have serum albumin in normal range.[45] Hence, a total of 74% of patients were having hypoalbuminemia in our study. In a study conducted by Morris *et al.*,[46] 72% were having hypoalbuminemia which is similar to our study. Hemoglobin level was below 7 g/dl (severe anemia) in 10.5% cases, between 7 g/dl and 8.9 g/dl (moderate anemia) in 20% cases, and between 9 g/dl and 11 g/dl (mild anemia) in 35.5% cases. Hence, a total of 66% of patients were anemic in our study. In a study conducted by Nagu *et al.*,[47] 86% were anemic which is similar to our study. In a study conducted by Olaniyi and Aken'Ova,[48] anemia occurred in 93.6% cases which are similar to our study.

CONCLUSION

Sputum positive TB patients have poor nutritional status. Malnutrition is found in individuals with factors of rural background, male patients, poor literary status, low family income, smoking, and alcohol addiction. Hence, we advise to increase the awareness among patients regarding the importance of nutrition and to discourage the addiction to improve the prognosis of TB patients and decrease the prevalence of TB. Macronutrient requirements in active TB like other infectious diseases are likely to increase energy requirement. Studies show that subjects who receive food supplements during TB treatment tend to gain more weight compared with those not receiving food supplements.

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Original Article

Effect of Pitavastatin in Patients with Active Rheumatoid Arthritis Treated at a Tertiary Care Hospital

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder, autoimmune in nature that predominately affects synovial joints. Being a crippling disease is a leading cause of disability that often reduces the quality of life and impairs patients ability to work.

Aims and Objectives: The aim of the study was to compare the effect of different treatment regimens on patients with active RA treated at a tertiary care hospital.

Materials and Methods: This was a prospective, open labeled, parallel arm, randomized, and single-center study performed in a tertiary care teaching hospital (Chennai Medical College Hospital and Research Centre [SRM Groups], Irungalur, Tiruchirapalli) and was conducted at outpatient clinics. Total duration of the study period was 24 weeks. All the patients were having active RA and were on oral methotrexate (first-line disease-modifying antirheumatic drug) at the time of recruitment.

Statistical Analysis: All the data were initially entered into Microsoft Excel 2010 and later these spreadsheets were used for analysis. Statistical analysis was done using SPSS version 20.0.

Conclusion: Combination therapy of pitavastatin and methotrexate is better than methotrexate monotherapy and combination therapy of rosuvastatin and methotrexate.

Key words: Combination therapy, Methotrexate, Pitavastatin, Rheumatoid arthritis, Rosuvastatin

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder, autoimmune in nature that predominately affects synovial joints. Being a crippling disease is a leading cause of disability that often reduces the quality of life and impairs patient's ability to work.[1] The primary goal of managing the patient with RA is to maximize long-term health-related quality of life and to achieve remission as soon as possible. Pharmacotherapy of RA involves symptom-modifying antirheumatic drugs such as nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs (DMARDs) – small molecule non-biological agents, biological agents, and glucocorticoids.[2] RA, if not treated properly, may lead to permanent damage to joints and is the number one cause of early retirement, disability payments, and loss of employment.[3]

The pleiotropic effects of statins such as anti-inflammatory, immune-modulating, and anabolic effects strongly support the potential role of these drugs in the prevention and/or treatment of cardiovascular risk factors and joint damage associated with RA.[4] Pitavastatin, the seventh statin reduces elevated levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein B, and triglycerides and increases high-density lipoprotein (HDL) cholesterol levels.[5] Pitavastatin has anabolic effect on bone and prevents osteoporosis induced by RA. Substantial cardiovascular protection offered by it can reduce cardiovascular morbidity and mortality associated with RA.[6,7] Rosuvastatin is a hydrophilic statin with extensive first-pass metabolism.

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The absorption of rosuvastatin is not affected by food and maximum plasma concentration is reached in 3–5 h. The usual dose is 5–10 mg once daily.[8] Important side effects include myopathy and rhabdomyolysis. It is contraindicated in hepatic failure, pregnancy, and lactation. It should be used cautiously in patients with diabetes since it increases the hemoglobin A_1C levels.[8] As an adjunct to DMARDs, rosuvastatin can effectively bring out remission in active RA patients. Only a limited number of studies elaborate the effect of pitavastatin in RA. Hence, this study was done to evaluate the efficacy and safety of pitavastatin in patients with active RA.

MATERIALS AND METHODS

Study Setting

This study was conducted at the Medicine Outpatient Department at Chennai Medical College Hospital and Research Centre, Irungalur, Tiruchirapalli.

Study Design

This was a hospital-based analytical cross-sectional study performed in a tertiary care teaching hospital (Chennai Medical College Hospital and Research Centre, Tiruchirapalli).

Sample Size

A total of 90 active RA patients who fulfilled the inclusion and exclusion criteria were recruited in the study after obtaining written informed consent. Study subjects were divided into three groups of 30 each.

Inclusion Criteria

Active RA patients of both the sexes in the age group of 20–60 years according to the American College of Rheumatology (ACR) criteria and on a dose of methotrexate 7.5 mg weekly for the past 3 months were enrolled for this study. Criteria for active RA include patients with more than or equal to six swollen joints/six tender joints (from 68 joint counts), C-reactive protein (CRP) more than or equal to 1.5 mg/dl, erythrocyte sedimentation rate (ESR) more than or equal to 28 mm at the end of 1st h, and morning stiffness more than or equal to 45 min.

Exclusion Criteria

Patients on steroids therapy, Vitamin D3 therapy, patients with severe RA as per ACR Criteria-Stage IV, pregnant and lactating women, patients with liver failure, renal failure, myopathies, and pancytopenia were all excluded from the study.

Sample Size

A total of 90 active RA patients who fulfilled the inclusion and exclusion criteria were recruited to participate in the study.

Data Collection Tool

Data collection was done during working hours at a time feasible to the respondents. The study was conducted in the hospital premises after obtaining prior permissions from the concerned authorities. After obtaining informed consent from the participants, they were divided into three groups, based on their treatment schedules and observed. The first group consisted of patients with RA with active disease on tab. Methotrexate 12.5 mg weekly, the second group included patients with RA with active disease on methotrexate 7.5 mg weekly + Tab. Rosuvastatin 10 mg once daily and in the third group included patients with RA with active disease on methotrexate 7.5 mg weekly + Tab. Pitavastatin 1 mg once daily. The respondents were asked to fill a questionnaire which covered information on socio-demographic data, biochemical parameters were measured by drawing 5 ml venous blood, the samples were collected from the subjects in all the three groups on 0th day at the end of 4th, 8th, and 12th weeks of the study period.

Parameters Measured

(i) Disease activity score (DAS): DAS was calculated according to the standard formula based on tender joint count, swollen joint count, ESR, and assessment of general health based on the scores between 0 and 100 from the patient. The joints involved and include shoulders, metacarpophalangeal joints, proximal interphalangeal joints, elbows, wrists, and knees of both sides contributing to a score of 28. Estimation was done at every visit. (ii) Rheumatoid factor (RF) test: RF test detects immunoglobulin M (IgM) antibodies to immunoglobulin G (IgG) antigen. The purified antigen is bound to a solid phase microassay well. Patient serum samples are diluted and added to each well. If antibody is present in the patient's serum, antigen-antibody complexes are formed. The absorbance of the solution, measured at 450 nm, is directly related to the concentration of IgM antibody. Values more than 7.7 IU are considered to be positive, with the presence of detectable antibodies. (iii) Anti-cyclic citrullinated peptide (CCP): Intended for the quantitative determination of IgG class antibodies directed against CCPs, present in human serum, or plasma. Procedure was the same as estimation of RF. The lowest concentration of anti-CCP detected is 1.12 U/ml with 98% confidence value. The immunological parameters, namely, RF and anti-citrullinated protein antibody were estimated by enzyme-linked immunosorbent assay. (iv) ESR: ESR was measured by Westergren method as the method of choice. The Westergren method uses ethylenediaminetetraacetic acid as an anticoagulant. The reference range is for men <15 mm/h–20 mm/h and for women <20 mm/h–30 mm/h. (v). Lipid profile: Lipid profile included total cholesterol, triglycerides, HDL, and LDL.

Statistical Analysis

The data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) (version 21.0) software package. Descriptive statistics were used to define the study population. Categorical and ordinal variables were expressed as frequency/percentages. Continuous variables were expressed as mean and standard deviation. Appropriate tests of significance (analysis of variance) were applied to the study variables to establish the relationship between the study variables. $P < 0.05$ was considered to be statistically significant.

RESULTS

Our results showed that among the study participants, more than half were female 59 (65.6%). Majority of the sample population, 37 (41.1%) respondents were in the age group of 41–50 years followed by 32 (35.6%) who were between the age group 51–60 years. The mean age group of the respondents was 48.32 ± 7.49 [Table 1].

Table 1: Age and gender distribution of the respondents (*n*=90)

Variable	Frequency	Percentage
Gender		
Male	31	34.4
Female	59	65.6
Age distribution		
30–40	19	21.1
41–50	37	41.1
51–60	32	35.6
>60	2	2.2
Mean age (±SD)	48.32±7.49	

Distribution of DAS Across the Three Groups at Various Time Periods

Our results showed that among the study participants the mean reduction in DAS were seen from the baseline at 4th, 8th, and 12th weeks of the study in all the groups and a significant reduction is seen in Group 3, having baseline value of 6.54–3.03 at the end of the study [Table 2]. This decrease in the DAS was found to be statistically significant ($P = 0.001$).

Distribution of Serum RF Levels Across the Three Groups at Various Time Periods

A mean reduction in RF was seen from the baseline to 12th week of study in all the groups and a significant reduction ($P = 0.003$) is seen in Group 3, having baseline value of 88.5–42.3 at the end of the study [Table 2].

Distribution of Serum Anti-CCP Levels Across the Three Groups at Various Time Periods [Table 2]

We found a mean reduction in anti-CCP level was seen from the baseline to 12th week of study in all the groups. In the third group, we found that the anti CCP values had decreased from 38.06 (at the begining of the study) to 18.33 (at the end of the study). There decrease in the serum anti-CCP levels was found to be statistically significant ($P = 0.001$).

ESR Across the Three Groups at Various Time Periods

As seen in Table 2, there has been a mean reduction in the ESR values among all the three groups. It has also been observed that only in the third group this reduction was found to be statistically significant.

Table 2: Distribution and comparison of various parameters among the respondents (*n*=90)

Variable	Group I	Group II	Group III	Test of significance* (ANOVA)
Disease activity score				
0 weeks	6.86±0.76	6.49±0.8	6.54±0.6	*P*=0.001
4 weeks	6.34±0.73	5.96±0.7	5.39±0.5	
8 weeks	5.96±0.75	5.56±0.7	4.14±0.5	
12 weeks	5.60±0.91	5.11±0.7	3.03±0.5	
Serum rheumatoid factor levels				
0 weeks	94.3±97.3	93.5±98.3	88.5±73.8	*P*=0.003
4 weeks	74.3±79.4	84.3±87.3	64.3±67.3	
8 weeks	64.2±68.5	66.3±69.3	54.3±57.5	
12 weeks	52.8±43.6	52.5±44.7	42.3±35.5	
Serum anti-CCP levels				
0 weeks	41.61±44.3	48.84±43.5	38.06±34.4	*P*=0.001
4 weeks	36.3±79.4	44.3±42.3	29.3±30.3	
8 weeks	28.2±68.5	32.3±29.3	23.4±26.5	
12 weeks	21.7±17.2	29.8±24.1	18.3±14.8	
ESR				
0 weeks	49.0±19.7	52.1±21.3	49.7±11.7	*P*=0.001
4 weeks	39.0±18.0	44.8±19.0	37.7±10.7	
8 weeks	34.2±16.2	39.7±17.8	27.6±8.4	
12 weeks	29.7±14.4	34.1±18.4	17.1±3.5	

*P<0.05 was taken to be statistically significant. ESR: Erythrocyte sedimentation rate, CCP: Citrullinated peptide, ANOVA: Analysis of variance

Table 3: Distribution and comparison of mean lipid profile values and Vitamin D values among the respondents (*n*=90)

Variable	Group I	Group II	Group III	Test of significance* (ANOVA)
Total cholesterol levels				
0 weeks	160.13±24.24	169.47±17.87	156.13±18.89	*P*=0.001
4 weeks	159.67±23.77	168.95±17.91	154.93±18.65	
8 weeks	159.33±23.68	168.18±18.17	153.65±18.68	
12 weeks	159.73±23.81	167.35±18.57	152.63±18.30	
TGL levels				
0 weeks	170.3±23.0	189.0±33.2	182.9±24.0	*P*=0.001
4 weeks	169.3±22.3	188.5±33.7	180.4±23.9	
8 weeks	168.9±22.9	187.7±34.5	178.0±23.2	
12 weeks	168.3±22.0	186.6±35.5	175.5±23.4	
LDL levels				
0 weeks	124.5±21.8	119.7±36.3	132.3±19.2	*P*=0.001
4 weeks	123.8±22.0	118.1±36.0	129.6±18.4	
8 weeks	123.8±21.7	115.7±35.0	126.6±18.0	
12 weeks	124.5±21.9	113.0±34.5	123.2±17.1	
HDL levels				
0 weeks	33.33±1.77	37.73±23.04	35.79±3.41	*P*=0.001
4 weeks	32.87±1.78	37.76±23.08	36.45±3.03	
8 weeks	32.90±1.94	37.78±23.08	37.00±3.15	
12 weeks	32.83±1.74	37.89±22.99	37.87±2.91	

*$P<0.05$ was taken to be statistically significant. TGL: Triglycerides, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Comparison of Mean Lipid Profile Values [Table 3]

Our results showed a uniform reduction in all the lipid profile values across all the three groups in the progressive weeks, except for HDLs which showed a significant increase. There was a significant reduction in total cholesterol, triglyceride, and LDL levels in all the three groups in the progressive weeks, as shown in Table 3.

DISCUSSION

RA is a chronic inflammatory, autoimmune disease which leads to rapid onset of clinically significant functional impairment, particularly if not controlled properly by DMARDs. Statins, because of their pleiotrophic effects, have been used in various trials to prove their efficacy in RA. The present study was conducted to find out the effect of pitavastatin in active RA patients along with methotrexate, compared to methotrexate monotherapy and methotrexate, rosuvastatin combination therapy.

The reduction in mean DAS was maximum among the subjects under pitavastatin + methotrexate group. Hence, pitavastatin and methotrexate combined therapy is superior to methotrexate monotherapy and combined therapy with rosuvastatin and methotrexate in reducing the DAS scores. This result is comparable with the result of Kumar *et al.*,[9] but against the studies conducted by Mikhael[10] McCarey *et al.*[11] and Das *et al.*[12]

The reduction in mean RA factor levels was maximum among the subjects under pitavastatin + methotrexate group followed by subjects under rosuvastatin and methotrexate. This correlates with the studies conducted by Abeles and Pillinger[13] Chan *et al.*,[14] and Niwa *et al.*[15]

The reduction in mean anti-CCP levels was maximum among the subjects under pitavastatin + methotrexate group followed by subjects under rosuvastatin and methotrexate. Hence, pitavastatin and methotrexate combined therapy is superior to methotrexate monotherapy and combined therapy with rosuvastatin and methotrexate in reducing the mean anti-CCP levels. This correlates with the findings from studies conducted by Abeles and Pillinger[13] Chan *et al.*,[14] and Niwa *et al.*[15]

The reduction in mean ESR levels was maximum among the subjects under pitavastatin + methotrexate group followed by subjects under rosuvastatin and methotrexate. This shows that pitavastatin and methotrexate combined therapy is superior to methotrexate monotherapy and combined therapy with rosuvastatin and methotrexate in reducing the mean ESR levels. This reduction in the ESR levels can be compared with the studies done by Kumar *et al.*,[9] Mikhael[10] McCarey *et al.*,[11] and Das *et al.*[12]

The LIVES study,[16] CHIBA study,[17] and PATROL trial[18] have shown a significant reduction in total cholesterol levels, triglyceride levels, and LDL levels with the combined therapy of pitavastatin + methotrexate. The have also documented a significant increase in the HDL levels. These findings are similar to the findings from our study. The highlight of the present study is the identification of superiority of pitavastatin as an adjuvant therapy along with

methotrexate in the management of patients with active RA with marked inflammation.

CONCLUSION AND RECOMMENDATIONS

Pitavastatin decreases the DAS and improves the well-being of patients with active RA by lowering the RFs and anti-CCP levels. It significantly reduces inflammation in active RA which is evident from the decrease in the ESR and CRP levels. Further the side effects such as myopathy and precipitation of diabetes seen with others statins are not that much pronounced while using pitavastatin. Further it raises the HDL level, lowers TG, TC, and LDL levels and has a favoring effect in reducing the cardiovascular risk factors. Considering the increasing morbidity and mortality in crippling disease-RA, particularly involving the cardiovascular system, addition of a potent statin like pitavastatin as an adjuvant to DMARDs can improve the quality of life of patients suffering from RA.

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Original Article

Outcome of Patients with Locally Advanced Rectal Cancer Treated with Neoadjuvant Chemotherapy and Radiotherapy

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Abstract

Introduction: About 30% of all colorectal tumors develop in the rectum. The location of the rectum within the bony pelvis and its proximity to vital structures presents significant therapeutic challenges when considering neoadjuvant options and surgical interventions. Neoadjuvant therapy may comprise either radiotherapy (RT) alone or in combination with chemotherapy. Commonly prescribed chemotherapy agents include 5-fluorouracil and oxaliplatin. These agents act to limit tumor cell division in several ways.

Aim: The aim of this study was to study the outcome of patients with locally advanced rectal cancer treated with neoadjuvant chemotherapy and RT.

Materials and Methods: Patients with locally advanced pathologically confirmed adenocarcinoma of the rectum, without detectable distant metastasis at presentation, were included in this study. Patients underwent neoadjuvant chemotherapy and radiation therapy.

Results: In 67 patients, 63% of patients were female; Stage IIA cases were 69% followed by Stages IIB and IIC 10% in each. About 19% of patients underwent surgery and 81% of patients underwent neoadjuvant chemoradiation followed by reassessment for surgery. Overall survival in 3 years in this study was noted as 67.6%.

Conclusion: Neoadjuvant chemoradiation followed by radical surgery has shown very satisfactory results in the management of locally advanced rectal cancers.

Key words: Chemoradiation, Chemotherapy, Neoadjuvant therapy, Rectal cancer

INTRODUCTION

Cancer of the rectum is less frequent than colon cancer, accounting for 5% of malignant tumors, and ranks as the fifth most common cancer in adults.[1,2]

In India, the annual incidence rates (AARs) for colon cancer and rectal cancer in men are 4.4 and 4.1/100,000, respectively. The AAR for colon cancer in women is 3.9/100,000. Colon cancer ranks 8th and rectal cancer ranks 9th among men. For women, rectal cancer does not figure in the top 10 cancers, whereas colon cancer ranks 9th.[3]

Colorectal cancer most commonly occurs sporadically and is inherited in only 5% of cases.[4] Migrant studies indicate that when populations move from a low-risk area (e.g., Japan) to a high-risk area (e.g., the USA), the incidence of colorectal cancer increases rapidly within the first generation of migrants, and Japanese born in the USA have a higher risk than the white population.[5] Diet is definitely the most important exogenous factor identified up to now in the etiology of colorectal cancer. It has been estimated that 70% of colorectal cancers could be prevented by nutritional intervention;[6] various promoting and protective factors have been identified in prospective and case–control studies. Evidence that diets rich in vegetable protect against colorectal cancer is substantial. Among subgroups of vegetables, green leafy vegetables were associated with a lower risk of colorectal cancer for

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men, while intake of fruits was not related to the risk of colorectal cancer in men or women.[7,8]

Colon and rectal cancers are usually considered one disease in the advanced setting because the prognosis and sensitivity to antineoplastic agents are largely similar for tumors originating from different portions of the large bowel. However, the pattern of recurrence of the colon and rectal cancers differs substantially. The final outcome of rectal cancer depends far more on the skills of the surgeon than for colon cancer. Chemotherapy is given with adjuvant intent to high-risk patients with both neoplasms, but in general, radiation therapy is also necessary for rectal cancer, while it is not in colon cancer.

Aim

The aim of this study was to study the outcome of patients with locally advanced rectal cancer treated with neoadjuvant chemotherapy and radiotherapy (RT).

MATERIALS AND METHODS

This observational study was conducted in the Department of RT at Thanjavur Medical College. Patients with locally advanced pathologically confirmed adenocarcinoma of the rectum, without detectable distant metastasis at presentation, were included during the period from November 2018 to October 2019.

Patient details were collected, complete clinical examination and rectal examination were performed. Hematology, biochemistry, colonoscopy, histopathology, computed tomography scan, and carcinoembryonic antigen were performed.

Patients underwent for the 1st cycle of chemotherapy with mitomycin C and 5-fluorouracil (5-FU) from day 1 to day 5 followed by RT. At 30 Gy of RT, patients received the 2nd cycle of chemotherapy with 5-FU (×5 days) only. RT was continued to a total of 50 Gy. Patients were reassessed 6 weeks after the end of chemoradiation for surgery. In suitable patients, either an abdominoperineal resection or low anterior resection was done, depending on the clinical situation. Following surgery, they received adjuvant 5-FU-based chemotherapy, once in 3 weeks, to a total of 6 cycles.

Radiation was given with telecobalt therapy, delivering 200 cGy per fraction, to a total dose of 50 Gy to the whole pelvis after simulation.

The 1st cycle of chemotherapy included inj. mitomycin C at a dose of 6 mg/m^2 intravenous (IV) on day 1 and inj. 5-FU at a dose of 375 mg/m^2 IV on day 1–day 5 in the 2nd cycle, inj. mitomycin C was not given.

RESULTS

In this study, 67 patients with locally advanced (T2-T4/N0-N2 disease), pathologically confirmed adenocarcinoma of the rectum, without detectable distant metastasis, were included in the study. The age of these patients varied

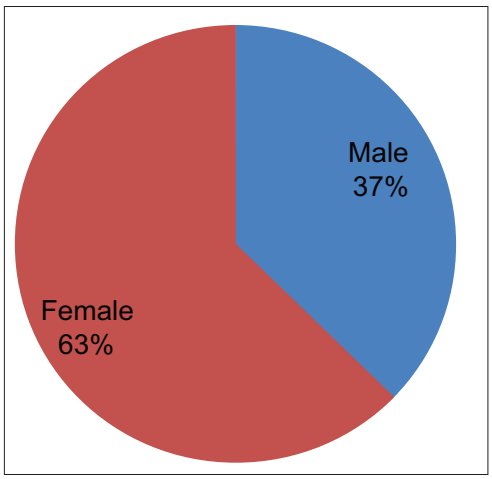

Figure 1: Gender distribution

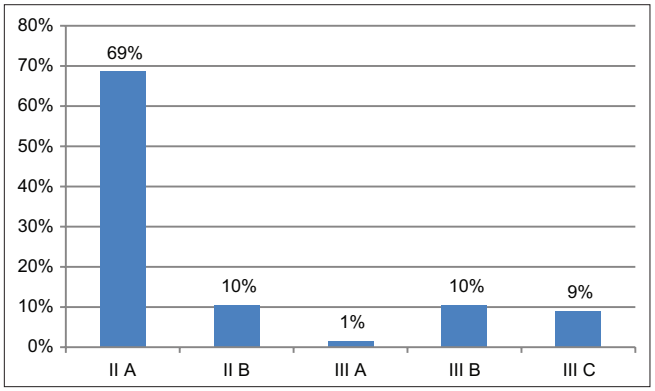

Figure 2: Stage distribution

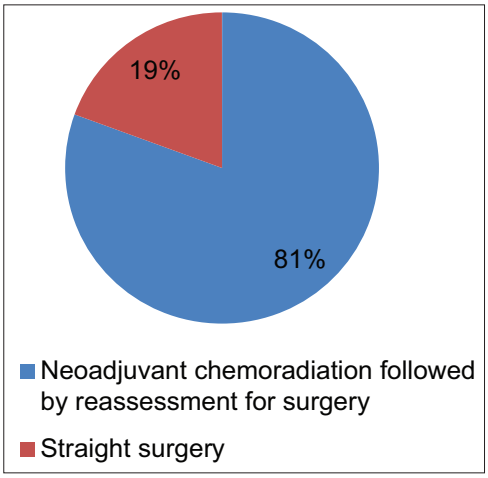

Figure 3: Treatment distribution

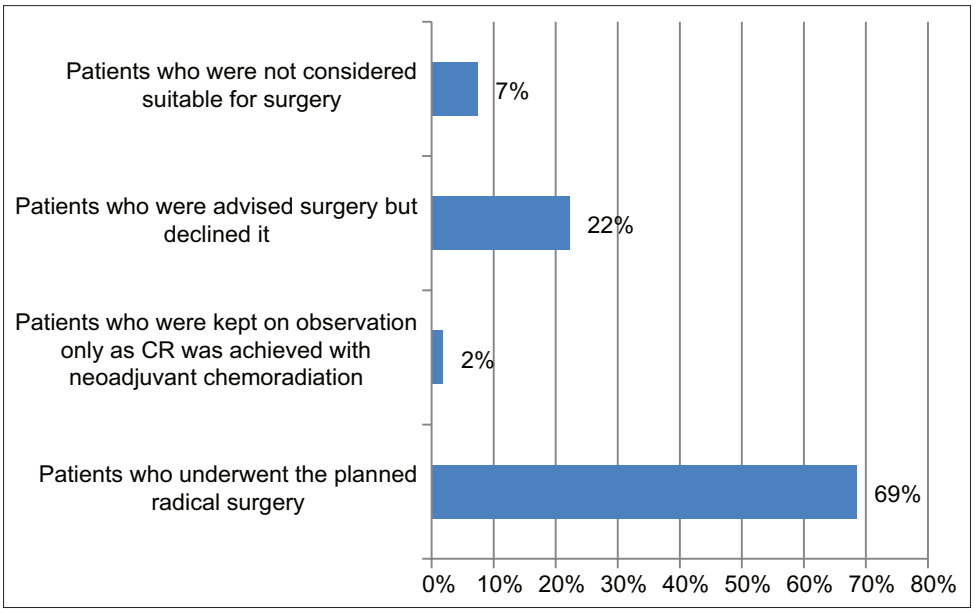

Figure 4: Patients completed neoadjuvant chemoradiation

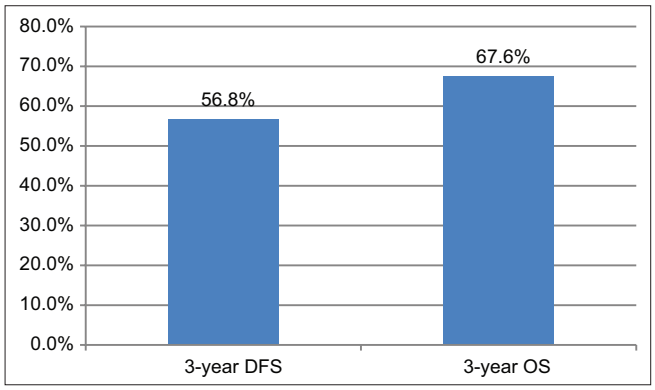

Figure 5: Outcome distribution

from 26 years to 78 years. The majority of the patients were female in our study (63%) Figure 1. Stage IIA cases were 69% followed by Stages IIB and IIC 10% in each Figure 2. About 19% of patients underwent surgery and 81% of patients underwent neoadjuvant chemoradiation followed by reassessment for surgery Figure 3. About 69% of patients underwent the planned radical surgery. 22% of patients who have advised surgery but declined it, 7% of patients who were not considered suitable for surgery Figure 4. Overall survival in 3 years in this study was noted as 67.6% Figure 5.

DISCUSSION

Colon and rectal cancers are usually considered one disease in the advanced setting because the prognosis and sensitivity to antineoplastic agents are largely similar for tumors originating from different portions of the large bowel. However, the pattern of recurrence of the colon and rectal cancers differs substantially. The final outcome of rectal cancer depends far more on the skills of the surgeon than for colon cancer. Chemotherapy is given with adjuvant intent to high-risk patients with both neoplasms, but in general, radiation therapy is also necessary for rectal cancer, while it is not in colon cancer.

Several cytotoxic agents act as radiosensitizers and hence increase the cytotoxic effect of RT. When used as adjuvant treatment, combined chemo-RT reduces the local recurrence rate and improves survival compared with RT alone. Moreover, chemotherapy may also have an effect on micrometastases and thereby reduce the frequency of distant metastases. However, cytotoxic agents also increase the side effects of RT, especially regarding the small bowel. Several drugs are being used, but 5-FU is the main component; the optimal time schedules have not yet been defined. In this respect, the continuous 5-FU infusion has been shown to be more effective than bolus 5-FU.[9] The results of a trial (INT 0144) evaluating the benefit of continuous infusion 5-FU during the entire 6 months adjuvant program versus continuous infusion 5-FU only during the period of RT do not show relevant differences between the three arms of the study.[10] Furthermore, there is no advantage of leucovorin or levamisole-containing regimens over bolus 5-FU alone when combined with irradiation. An open question has been whether radiochemotherapy is better when administered as adjuvant or neoadjuvant modality: Two trials in North America were conducted with the aim of evaluating the role of integrated strategy but were closed due to poor patient accrual. The preliminary results of the NSABP R03 trial and the German study strongly suggested a benefit for the pre-operative approach: The

neoadjuvant strategy was more active and demonstrated less risk for acute and late morbidity.[11,12]

CONCLUSION

The potential advantages of a pre-operative approach over a post-operative one are decreased tumor seeding during the operation, less acute, and late toxicity increased the efficacy of RT and, for patients who receive a conventional long course of RT, an increased rate of sphincter preservation. FU-based schemes in combination with pre-operative irradiation are employed with the aim of improving local control and reducing distant recurrence rates.

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Original Article

The Role of Attachment to Mother and Self-esteem toward Aggression Behavior in Depok City, Indonesia

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Abstract

Background and Purpose: Attachment is an emotional relationship that is built by the child and mother from birth and becomes one of the factors forming the child's behavior. One of the behaviors that can be related to mother-child attachment is aggression. Another thing that might help determine the emergence of aggression behavior in adolescents is self-esteem. This study aims to (1) determine the effect of attachment on mothers and self-esteem with aggression behavior in adolescents, (2) determine the effect of attachment on mothers with aggression behavior in adolescents, and (3) determine the effect of self-esteem with aggression behavior in adolescents.

Methodology: The subjects in this study were adolescents in PIT Junior High School in Depok city, totaling 130 students. The technique used is multiple regression techniques.

Results: The results showed $P = 0.01$ meaning that there was a strong significant relationship between the quality of attachment to the mother and self-esteem with aggression behavior. Partially, there is the influence of the quality of attachment to the mother with aggressive behavior at a fairly strong level with a negative direction ($R = -0.377$, $P = 0.01$), and there is an effect of self-esteem with the behavior of the aggression at a weak level with a negative direction ($R = -0.277$, $P = 0.01$), meaning that the lower the quality of attachment to the mother and self-esteem, the higher the aggression behavior. The quality of attachment to the mother and self-esteem contributed effectively to 28.6% of the behavior of aggression.

Conclusion: There is a strong significant effect between the quality of attachment to the mother and self-esteem with the behavior of aggression in adolescents in PIT Junior High School in Depok city. That is, the lower the quality of attachment to the mother and self-esteem, the higher the aggression behavior.

Key words: Aggression, Attachment, Self-esteem

INTRODUCTION

Aggressive behavior is a deviant behavior in adolescents. Negative family climate that is full of disputes and colored by more general conflicts can spread the atmosphere of the house which makes the atmosphere between family members uncomfortable so that it can cause teens to feel stress, insecurity, and discomfort. Teenagers in such an environment are at high risk of developing problematic behaviors such as aggressive, abusive behavior, and depression.

Hurlock (2005) defines aggression as a reaction of spontaneous anger, can be physical or verbal. This anger reaction is usually used by adolescents as an instrument of power over their environment. For example, teens will slam things when their desires are not fulfilled. The tendency to show aggressive behavior generally appears prominently starting from childhood so that social interaction that occurs in adolescents is usually characterized by aggressive behavior such as hostility, anger, shouting, slamming, and damaging objects. Not only that, when aggressive behavior occurs at school, this can make classmates become frightened and make the classroom not conducive anymore. Adolescents who behave aggressively at school and at home certainly cause concern for parents. Teens who behave

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aggressively have the potential to endanger themselves and others so that no parent wants their child to be a victim of aggressiveness or aggressors.

Murray (Hall and Lindzey, 1993) says that aggression is a way to overcome resistance strongly or punish others. Aggressive according to Baron (Cahya, 2018) is the behavior carried out by individuals with the aim of injuring or harming other individuals. Myers said that aggressive behavior was physical or verbal behavior to hurt others (Cahya, 2018).

Hall and Lindzey (1993) described any behavior that is an outlet for feelings of frustration to overcome resistance strongly or punish others, which is intended to injure others physically or psychologically to others that can be done physically or verbally called aggression.

Teenagers are a phase of development experienced by all humans. Adolescence means the development of a transition involving physical, cognitive, emotional, and social changes in various forms in different social, cultural, and economic backgrounds (Papalia and Feldman, 2015). Adolescence offers many opportunities for growth not only from the physical dimension but also in cognitive, emotional, autonomy, self-esteem, and intimacy competence. Adolescents who have supportive relationships with parents, schools, and communities tend to develop in positive and healthy ways (Papalia and Feldman, 2015).

The adolescent phase according to Monks, Knoers, and Hadinoto (2006) takes place between the ages of 12 and 21 years, with a division of 12–15 years of early adolescence, 15–18 years of middle adolescence, and 18–21 years of late adolescence. Stanley Hall explained that adolescence is a time filled with pressure and a period of upheaval influenced by conflict and mood swings (Santrock, 2007).

The social development of adolescents can be seen in the presence of two kinds of movements, namely, separating from parents and toward peers. De Wuffel explained that the quality of relationships with parents plays a very important role in the development of adolescence (Monks *et al*., 2006). Basically, the family is the smallest unit of society and has become the primary social institution for raising children. Brofenbrenner explained that the family environment (home), neighbors, schools, and workplaces are the smallest systems (microsystems) that can affect individual development (Papalia and Feldman, 2015). This shows how important the role of the family as one microsystem in the life of a teenager. The role of the family in influencing adolescent development is inseparable from the relationship between parents or caregivers with children in the home.

Relationships that are established in a family can form an emotional bond that is commonly known as attachment. Attachment is a bond that reinforces and is reciprocal, usually occurs between infants and caregivers (caregivers) who contribute to each other to build a quality relationship (Papalia and Feldman, 2015).

Bowbly argues that attachment can occur at any age level, as in the stages of adolescent development (Santrock, 2002). Children can learn about themselves by the attachment experience they get. Ainsworth (Helmi, 2004) defines attachment as an affective bond to someone who is aimed at a sticky figure and this bond lasts a long time and continuously. Furthermore, Ainsworth also explained that secure attachment in the 1st year provided an important foundation for future psychological development (Santrock, 2002).

The nature of adolescent attachment to parents determines a lot, insecure attachment (insecure attachment) if it occurs together with independence raises excessive attention to self-interest, while insecure attachment together with dependence leads to conformity orientation or full isolation of anxiety (Monks *et al*., 2006). According to Erikson, adolescents try to break away from parents with a view to finding themselves called the process of searching for ego identity (Monks *et al*., 2006). Development experts reveal the new role of attachment of parents in adolescents play an important role in the formation of behavior (Santrock, 2002).

Mother was ranked first as a teenage main stick figure. Mothers usually interact more with children and function as people who meet their needs and provide comfort (Eliasa, 2011). Parental attachment is an adaptive function that provides a foundation for adolescents to interact with the wider environment. According to Santrock (2002), a strong attachment can protect teens from anxiety and feelings of depression or emotional distress associated with the transition period between children to adults. Stickiness can make teens think that they have a warm family and can tell of any complaints they experience.

The quality of the relationship between parent and child is related to the ability to adapt to children during pre-school, elementary, and middle school. The results of Dallaire's research (Paramita and Soetikno, 2018) show that the more sensitive and responsive parents are in responding to their children need, the teenagers will increasingly develop a feeling of security in relation to their parents (securely attached). A strong tendency in children to attach

themselves to the father or mother can be interpreted as a way to reduce their potential to do something that can be harmful or hurtful behavior (Bowlby, 1988). This is corroborated in research conducted by Chang *et al.* (Sari *et al.*, 2018) which says that there is a positive correlation between negative parenting and the appearance of problematic behavior in children.

In addition to the attachment of mothers to adolescents, self-esteem is one factor that can also influence the occurrence of aggression behavior. Good self-esteem can help teens control their behavior, so they will think before doing something. Self-esteem is a term that is literally interpreted as self-esteem (Echols and Shadily, 1997). One of the pioneers who put forward the theory of self-esteem, Morris Rosenberg (Mruk, 2006) suggests that self-esteem is a positive or negative attitude of an individual toward a particular object called self. Rosenberg further explained that high self-esteem expresses the feeling that the individual is "good enough." Individuals will feel that individuals are valuable people; respecting him as he really is, but not admiring himself or hoping that others will be impressed with him. Individuals do not consider themselves superior to others.

Conversely, individuals with low self-esteem will have characteristics such as hypersensitivity, feeling unstable or insecure, insecure, more caring to protect themselves from painful things than to actualize opportunities and enjoy life, inability to take risks, have depressive symptoms general, pessimistic, lonely, and feelings of alienation that refer to one of the negative behaviors such as aggressive behavior (Rosenberg and Owens, in Mruk, 2006).

Based on the background described above, the problems that will be examined in this study are as follows: (1) Whether there is an effect of attachment to the mother and self-esteem with aggression behavior in adolescents, (2) whether there is an effect of attachment in mothers with aggression behavior in adolescents, and (3) whether there is an influence of self-esteem with aggression behavior in adolescents.

METHODOLOGY

The subjects in this study were adolescents who were registered as students of PIT Junior High School in Depok city, totaling 130 students. This study uses three types of scales as a measurement tool to obtain the necessary data provided directly on the research subject.

The Inventory of Parent and Peer Attachment (IPPA) scale is a scale used to measure the attachment between mother and child proposed by Armsden and Greenberg, in 1991 (Armsden *et al.*, 1991). The IPPA scale uses a Likert scale consisting of 25 items and provides four answer choices, including SS (strongly agree), S (agree), TS (disagree), and STS (strongly disagree). An example of the item is "I feel I need to know what my mother thinks about the things I think about." The trial results show 20 valid items with a reliability coefficient of 0.858.

Aggression behavior scale is used to measure aggression behavior. In this study, the scale of aggression behavior was used which was adapted from the scale of aggression Buss and Perry (1992). An example of the item is "If my friend is looking for problem with me, I can just hit him." The trial result shows 20 valid items with a reliability coefficient of 0.821.

Self-esteem is a form of positive attitude and giving appreciation from individuals toward themselves (Murk, 2006). In this study, the self-esteem scale was used which was adapted from the Rosenberg self-esteem scale (RSES) in 1965 (Albo *et al.*, 2007). An example of the item is "Sometimes, I feel that I'm not good at all." Test results show seven valid items with a reliability coefficient of 0.772.

This research is a multiple regression analysis study. Before conducting a hypothesis test, a basic assumption test and a classic assumption test are performed. Calculation of data analysis using a Statistical Product and Service Solutions (SPSS) computer program.

RESULTS

The basic assumption test results are normality for aggression behavior scale, IPPA scale, and RSES using one-sample Kolmogorov–Smirnov test, that is, 0.200 ($P > 0.05$), so it can be concluded that the data of this study are normally distributed.

Linearity test results show that the relationship between the variables of aggression behavior with the quality of attachment to the mother and between the variables of aggression behavior with self-esteem there is a linear relationship, with a linear variable of 0.000 ($P < 0.05$).

Multicollinearity test results for the variable quality of attachment to the mother and self-esteem variables have a tolerance value of 0.850 and a variance inflation factor (VIF) value of 1.176. Tolerance value is >0.1 and VIF value is <10. This means that there is no multicollinearity between independent variables.

Heteroscedasticity test results can be known with the help of SPSS showing the distribution of scatterplot images which in this study showed no clear patterns, and the points

Table 1: Multiple regression analysis

R	0.535
R^2	0.286
Uji F	25.430
Sig.	0.000

spread above and below the number 0 on the Y-axis; then, there was no heteroscedasticity, so it can be concluded that did not occur heteroscedasticity.

Furthermore, Table 1 summarized that based on the results of the study using multiple regression analysis, techniques obtained value of R = 0.535; calculated F = 25.430 and *P* = 0.01. These results indicate that there is a strong significant influence between the quality of attachment to the mother and self-esteem with aggression behavior. The results of this study are in accordance with the hypothesis put forward by researchers, that is, there is a strong significant effect between attachment to the mother and self-esteem with aggression behavior in adolescents. The two independent variables, namely, the quality of attachment to the mother and self-esteem together have an influence with the need for aggression in adolescents.

The value of $R^2 = 0.286$ which means that the variable quality of attachment to the mother and self-esteem together contribute up to 28.6% in the emergence of aggression behavior. The remaining 71.4% is by other variables not tested empirically in this study. Based on the results of this study, it can be concluded that the quality of attachment to the mother and self-esteem can be used as predictor variables to predict aggression behavior.

The second and third hypothesis test results in this study were conducted using a partial correlation test to determine the relationship between the two variables, namely, the independent variable and the dependent variable. It is known that the significance value on the partial test of aggression behavior variables and the quality of attachment to the mother is 0.000 ($P < 0.05$) with R = −377. This shows that the second hypothesis is accepted, which means that the influence between the qualities of attachment to the mother with aggressive behavior is at a fairly strong level. The direction of the formed influence is negative, which means the lower the quality of attachment to the mother, the higher the aggression behavior, so it can be concluded that there is a negative and significant effect between the qualities of attachment to the mother with aggression behavior. Furthermore, based on the results of the partial correlation test on the variables of aggression and self-esteem behavior, a significance value of 0.001 ($P < 0.05$) with R = −0.277 is known. This shows that the third hypothesis is accepted which means that the influence between self-esteem and aggression behavior is at a weak level. The direction of the formed behavior is negative which means the lower the self-esteem, the aggression behavior will be higher, so it can be concluded that there is a negative and significant difference between self-esteem and aggression behavior.

The result of the significance value of 0.000 on the attachment variable <significance of 0.001 on the self-esteem variable ($P < 0.05$) indicates that the attachment variable is more influential than the self-esteem variable in predicting aggression behavior in adolescents.

DISCUSSION

Attachment to the mother is needed throughout the lifetime of the child, this is very important for children (Santrock, 2014). The mother is ranked first as the child's best stick figure. Mothers usually interact more with children and function as people who meet their needs and provide comfort (Eliasa, 2011). The quality of attachment to a good mother will affect adolescents in interacting with the surrounding environment. Stickiness gives teens emotional security. The sense of security that has developed since childhood will underlie its success in establishing social relationships in the future. Conversely, when children who have become teenagers do not have a trust in the environment, adolescents will feel afraid to relate to others, under certain conditions will lead to aggression behavior.

The results of the analysis mean that insecure attachment has a positive relationship with the form of aggression, meaning that the more a person insecure, the higher the aggression behavior as revealed in the Dubois-Comtois (2013) study. In addition, the analysis also means that secure attachment can help reduce the level of aggression. This result is in line with Savage (2014) and Moretti and Peled (2004) research which states that secure attachment is associated with low aggression behavior in children and adolescent involvement in harmful behavior.

Good self-esteem can help teens control their behavior, so they will think before doing something. Conversely, individuals with low self-esteem will have characteristics such as hypersensitivity, feeling unstable or insecure, insecure, more caring to protect themselves from painful things than to actualize opportunities and enjoy life, inability to take risks, have depressive symptoms general, pessimistic, lonely, and feelings of alienation that refers to one of the negative behaviors such as aggressive behavior (Rosenberg and Owens, in Mruk, 2006).

Based on the results of research and discussion that has been described, researchers have answered research

hypotheses regarding aggression behavior in adolescents in terms of the quality of attachment to the mother and self-esteem in students of PIT Junior High School in Depok city simultaneously. This is supported by other researches which say that insecure attachment with mothers contributes effectively to aggression by 16.5% of 388 students of SMAN 2 Ungaran (Tungga and Desiningrum, 2018).

However, this study is inseparable from the limitations that research can only be generalized to a limited extent in the study population, namely, students of PIT Junior High School in Depok city so far application to a wider population with different characteristics requires further research. It is hoped that further research can find more comprehensive results by expanding the scope of research and also adding other psychological variables.

In addition to limitations and weaknesses, this study also has several advantages that can be considered as a reference source for research related to aggression behavior. This research can prove the proposed hypothesis, namely, the quality of attachment to the mother and self-esteem affect the behavior of aggression in adolescents in PIT Junior High School in Depok city. This research can be used as a reference to strengthen existing theories. In addition, this study is accompanied by additional analysis that can provide more information for readers. Another advantage is that this research can increase the awareness of readers, especially students, parents, and the school of the importance of raising awareness of aggression behavior due to its detrimental effects on actors, others, and the environment.

CONCLUSION

Based on the results of the study, it can be concluded that there is a strong significant influence between the quality of attachment to the mother and self-esteem with the behavior of aggression in adolescents in PIT Junior High School in Depok city. Furthermore, there is an influence between the qualities of attachment to the mother with aggressive behavior at a quite strong level with a negative direction in adolescents in PIT Junior High School in Depok city. This means that the lower the quality of attachment to the mother, the higher the aggression behavior. In addition, there is also an influence between self-esteem and aggression behavior at a weak level with a negative direction in adolescents in PIT Junior High School in Depok city. This means that the lower the self-esteem, the higher the aggression behavior. The quality of attachment to the mother and self-esteem contributes effectively to 28.6% of the behavior of aggression in adolescents in PIT Junior High School in Depok city.

SUGGESTION

Through the above review, researchers suggest that teens can train themselves in controlling emotions, for example, with deep breathing techniques such as regulating deep breathing while counting the numbers 1–10 repeatedly while feeling emotions that lead to aggression behavior until the emotions subside and disappear. In addition, adolescents can divert excessive emotional drive for more positive things such as being active in joining extracurricular activities at school or sports activities. Furthermore, for parents, this study presents that attachment with parents, especially in mothers, can help reduce the level of aggression in adolescents. Therefore, active parental roles are needed to build secure attachments to adolescents so that aggression behavior that leads to deviation can be prevented, for example, by being supportive and sensitive to the needs of adolescents, building good communication within the family, and make teens feel safe and trust in parents. For further researchers to be able to develop other psychological variables outside the variables that have been used in this study such as friendship variables or school environment variables. In addition, it is also suggested that conducting research with a larger population so that research generalizations will become wider.

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Original Article

A Study of Lipid Profile in Non-diabetics with Stroke

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Abstract

Aim: The aim is to study the serum lipid profile in non-diabetics with stroke and to determine the significant correlation between them.

Materials and Methods: A cross-sectional study was conducted on patients period of 12 months from May 2018–June 2019, Mahatma Gandhi Memorial Hospital for 6 months. Patients and controls were tested for fasting lipid profile 12 h after overnight fast. Participants were 60 patients of non-diabetic stroke and 60 controls. Among the 60 patients, 37 were male and 23 were female. In controls, there were 37 males and 23 females. Age- and sex-matched controls were selected. Stroke patients with infarct or hemorrhage in computed tomography brain were included in the study.

Results: In this study, total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and triglycerides were significantly associated with the risk of stroke. In this study, 56.7% of patients had high-density lipoprotein <40 mg/dl, 41.7% had TC >200 mg/dl, 65% of them had LDL cholesterol >100 mg/dl, and 43.3% of patients had very LDL >30 mg/dl.

Key words: Dyslipidemia, Lipid profile, Non-diabetic stroke

INTRODUCTION

Stroke or a cerebrovascular accident is an acute neurological injury which occurs due to vascular pathology and presents as a brain infarction or hemorrhage. Stroke is a medical emergency. The risk factors of stroke have been identified. The modification of risk factors in stroke has brought down both mortality and morbidity of stroke remarkably in the past 30 years.

Dyslipidemia, as a major risk factor for stroke, is studied for many years. Various studies in different population have shown dyslipidemia that is associated with stroke. Dyslipidemia is a correctable risk factor. It has been shown that the reduction of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, triglycerides, very LDL (VLDL) cholesterol, and increasing high-density lipoprotein (HDL) cholesterol by drugs has decreased the incidence of stroke.

In our study, lipid profile was studied in non-diabetic patients with stroke. Diabetes itself is associated with hyperlipidemia and increased atherosclerosis which makes it an undisputed risk factor for stroke. The atherogenicity of diabetics and non-diabetics is different. Hence, non-diabetic patients were included in the study.

The study is titled as "A STUDY OF LIPID PROFILE IN NON-DIABETICS WITH STROKE."

Aim

This study aims to study the serum lipid profile in non-diabetics with stroke and to determine the significant correlation between them.

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MATERIALS AND METHODS

The study was conducted on 60 non-diabetic stroke patients and 60 age- and sex-matched controls who did not have a stroke after obtaining informed consent.

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This is a cross-sectional study conducted over a period of 6 months in Mahatma Gandhi Memorial Hospital. Detailed history, clinical examination, radiological examination, serum TC, LDL, VLDL, HDL, and triglycerides were estimated by enzymatic method.

Inclusion Criteria

All patients with stroke with hemorrhage or infarct in computed tomography brain were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

- Patients with diabetes mellitus
- Patients on drugs for dyslipidemia
- Patients on dietary modification for dyslipidemia cerebral infarct associated with trauma or tumor.

Collection of Blood Sample

Blood samples were collected from all patients after an overnight fast of minimum 12 h. The previous day patient was advised to have light fat-free diet. Sample collected from cubital fossa. Tourniquet was released just before sample collection to avoid increased serum lipids artifactually. Ten milliliters of blood were drawn in sterile syringes and blood was transferred to dry glass tubes.

Preparation of Serum

Serum for HDL was separated within 2 h of collection. The sample was centrifuged at 5000 rpm for 10 min in a centrifuge tube. The clear serum was pipetted out and stored at 4°C. Samples were analyzed within 24 h.

Serum TC Estimation

Serum TC is measured by cholesterol peroxidase method. This method has extended stability. Reconstituted reagent is stored at 2–8°C and is stable for 90 days. This method is linear up to 500 mg/dl.

Table 1: Preparation of working reagent

Parameter	Blank	Standard	Sample
Working reagent	1000 µL	1000µL	1000µL
Standard	-	10 µL	-
Sample	-	-	10 µL

Table 2: Procedure

Sample	300 µL
High-density lipoprotein reagent	300 µL

Table 3: Working Reagent

Parameter	Blank	Standard	Sample
Working reagent	1000 µL	1000 µL	1000 µL
Standard (HDL)	-	50 µL	-
Sample (HDL supernatant)	-	-	50 µL

HDL: High-density lipoprotein

Principle

Enzymatic calorimetric method of the determination of TC is by the following reactions:

$$\text{Cholesterol} + \text{water} \xrightarrow{\text{Cholesterolesterase}} \text{fattyacid} + \text{cholesterol}$$

$$\text{Cholesterol} + \text{oxygen} \xrightarrow{\text{Cholesterolesterase}} 4\text{-cholesten-3-one} + H_2O_2$$

$$2H_2O_2 + \text{phenol} + 4\text{-aminoantipyrine} \xrightarrow{\text{Peroxidase}} \text{redquninone} + 4H_{20}$$

The reagent is stable when stored at 2–8°C up to expiry date. The reagent is linear up to the value of 500 mg/dl, if the concentration is >500 mg/dl, the sample has to be diluted with normal saline and the assay has to be repeated and the result has to be repeated with dilution fraction.

Reagents

- CHOLESTEROL R1: 2 ml × 50 ml/4 ml × 50 ml/4 ml ×100 ml/2 ml × 405 ml Phenol – 24 mmol/L
  - Sodium cholate – 0.2 mmol/L Sipes buffer
  - pH (6.9) – 50 mmol/L.
- CHOLESTEROL R2: 2 ml × 50 ml/4 ml × 50 ml/4 ml × 100 ml/8 ml × 100 ml
  - Cholesterol esterase >200 U/L
  - Peroxidase >1000 U/L
  - Cholesterol oxidase <250 U/L
  - 4-aminoantipirine – 0.5 mmol/L.
- CHOLESTEROL STANDARD: 1 ml × 5 ml/1 ml × 5 ml/1 ml × 5 ml/2 ml × 5 ml.
  - Cholesterol standard concentration 200 mg/dl.

Preparation of Working Reagent

Dissolve reagent R1 and R2 of cholesterol is shown on the label sample – serum.

Mix the contents and incubate at 37°C for 5 min. Absorbance of the standard and sample to be measured against reagent blank.

Table 4: Preparation of working reagent

Parameter	Blank	Standard	Sample
Working reagent	1000 µL	1000 µL	1000 µL
Standard	-	10 µL	-
Sample	-	-	10 µL

Table 5: Sex X diagnosis

Gender	Non-diabetics with stroke	Control
Male	61.7	61.7
Female	38.3	38.3

Calculation

Cholesterol conc. (mg/dl) = Absorbance of sample/absorbance of standard × 200.

Estimation of Serum HDL Cholesterol

The reagent measures HDL cholesterol in serum/plasma by precipitation method, linear up to 125 mg/dl.

Reagent Composition

- HDL CHOLESTEROL REAGENT: 4 ml × 25 ml
  - Magnesium chloride – 1 mmol/L
  - Phosphotungstate – 14 mmol/L.
- HDL CHOLESTEROL CONCENTRATION STANDARD – 1 ml × 5 ml
- HDL CHOLESTEROL CONCENTRATION: 50 mg/L.

Principle

VLDL, LDL, and chylomicrons are precipitated by magnesium and phosphotungstate. HDLs are concentrated in the supernatant; the following centrifugation is measured by enzymatic methods.

Reagent

Reagent is stored at 2–8°C and is stable up to expiry date. The reagent is linear up to the value of 125 mg/dl, if the concentration is >125 mg/dl, the sample has to be diluted with normal saline and the assay has to be repeated and the result has to be repeated with dilution fraction.

The reagent can be used readily.

Sample: Serum/plasma.

Procedure

Mix both reagent and sample allow it to stand for 10 min at room temperature. Remix and centrifuge for 10 min at 4000 rpm. Separate the clear precipitant within 1 h and HDL cholesterol concentration has to be determined.

Mix the contents and incubate at 37°C for 5 min. Absorbance of the standard and sample to be measured against reagent blank.

Calculation

HDL cholesterol conc. (mg/dl) = Absorbance of sample/absorbance of standard × N ×2.

- Where, 2 is dilution factor of sample
- N is the standard concentration.

Serum LDL

The immunological principle together with enzymatic assay of cholesterol is used for estimation of LDL directly.

LDL = TC–(HDL cholesterol+triglyceride/5).

Serum Triglyceride

Glycerol phosphate oxidase-p-aminophenazone methodology is used for measuring triglycerides in serum or plasma.

Reagent is stored at 2–8°C and is stable up to expiry date. The reagent is linear up to the value of 1000 mg/dl, if the concentration is >1000 mg/dl, the sample has to be diluted with normal saline and the assay has to be repeated and the result has to be repeated with dilution fraction.

Principles

Enzymatic determination of triglycerides is by the following reaction:

$$\text{Triglyceride} + \text{water} \xrightarrow{\text{Lipoproteinlipase}} \text{glycerol} + \text{fattyacid}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{Glycerolkinase}} \text{glycerol} - 3 - \text{phosphate} + \text{ADP}$$

$$\text{Glycerol3phosphate} + \text{oxygen} \xrightarrow{\text{Glycerol3phosphateoxidase}} \text{dihydroxylacetonephosphate} + H_2O_2$$

$$H_2O_2 + 4 - \text{aminoantipirine} + \text{P} - \text{chlorophenol} \xrightarrow{\text{POD}} \text{redquinoneimine}$$

TRIGLYCERIDESTANDARDCONCENTRATION – 200 mg / dl

Sample – serum/plasma.

Mix the contents and incubate at 37°C for 5 min. Absorbance of the standard and sample to be measured against reagent blank.

Triglyceride concentration (mg/dl) = Absorbance of sample/absorbance of standard ×200

VLDL concentration (mg/dl) = Triglyceride/5.

Age X Diagnosis

In both control groups and people with non-diabetic stroke, <40 years are 8.3%. In 41–60 years, it is 48.3% and >60 years is 43.3%. Maximum number of patients in 41–60 years group is 48.3%.

Sex X Diagnosis

In both groups, 61.7% of the patients were male and 38.3% were female. Male-to-female ratio is 1.61:1.

Body Mass Index X Diagnosis

Body mass index	Non-diabetics with stroke	Control
Underweight	1.7	0
Normal	46.7	66.7
Overweight	50	33.3
Obese	1.7	0

In non-diabetics, 1.7% was undernourished, 46.7% was normal, 50% overweight, and 1.7% obese. Maximum number of patients – 50% was overweight. In control, 66.7% was normal and 33.3% was overweight.

Smoking X Diagnosis

Smoking	Non-diabetics with stroke	Control
Yes	23.3	0
No	76.7	100

In non-diabetics with stroke, 23.3% were smokers and 76.7% were non-smokers. In control group, 100% were smokers.

Hypertension X Diagnosis

Table 6 shows that 23.3% of non-diabetics with stroke had hypertension and 76.7% of the same group were normotensives. All controls 100% were normotensives.

TC X Diagnosis

About 43.3% of non-diabetics with stroke have TC < 200 About 16.7% of the same group had cholesterol 200–240. About 40% of the same group has cholesterol more than 240%. Maximum patients, 43.3% has normal levels of TC. In controls, 90% have normal cholesterol values <200. About 5% has cholesterol 200–240. About 5% has cholesterol more than 240.

Triglycerides X Diagnosis

Triglycerides	Non-diabetics with stroke	Control
<150	58.3	86.7
150–199	26.7	6.7
>200	15	6.7

Table 6: Hypertension X diagnosis

Hypertension	Non-diabetics with stroke	Control
Yes	23.3	0
No	76.7	100

Table 7: Total cholesterol X diagnosis

Total cholesterol	Non-diabetics with stroke	Control
<200	43.3	90
200–240	16.7	5
>240	40	5

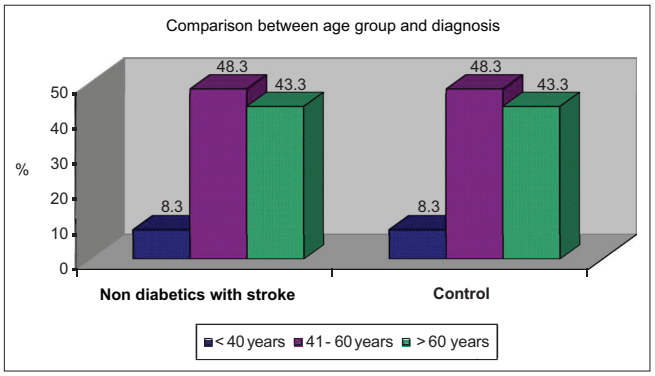

Figure 1: Age X diagnosis

In non-diabetics with stroke, <150 triglyceride value was 58.3%; 150–199 was 26.7%; and >200 was 15%. Maximum patients, 58.3% has normal triglycerides. In controls, 86% has triglyceride <150, 6% has 150–199%, and in 6% more than 200. Maximum controls, 86% has normal triglyceride values.

In non-diabetics with stroke, 53.3% had HDL cholesterol <40 and 46.7% had HDL cholesterol >40%. Maximum number of patients 53.3% had low HDL cholesterol. In control group, 36.7% had HDL <40 and 63.3% had HDL >40%. Maximum number of controls 63.3% had normal HDL values.

In non-diabetics with stroke, 71.7% had HDL/LDL ratio <0.39. Only 28.3% of the same group had HDL/LDL ratio >0.4%. In control group, 83.3% had HDL/LDL ratio >0.4 and 16.7% had HDL/LDL ratio >0.4.

In non-diabetic stroke males, 56.8% has TC/HDL >4.5 and 43.2% has <4.4. Maximum number of patients had TC/HDL ratio. In the control group, 86.5% has TC/HDL ratio in males <4.4 and 13.5% had >4.5.

In non-diabetic stroke with females, maximum number of patients had 78.3% TC/HDL ratio >4 and 21.7% had ratio <3.9%. In the control group, maximum number of controls, 65.2% has TC/HDL <3.9. 35.8% has TC/HDL more than 4.

In non-diabetics with stroke, 56.7% had VLDL <30 and 43.3% had VLDL >30%. Maximum number of patients has VLDL normal values. About 86.7% of controls had normal VLDL <30%. About 13.3% of controls have high VLDL values >30 [Figure 1 and Tables 1-7].

DISCUSSION

Association of TC to Non-diabetics with Stroke

In our study conducted on 60 patients showed TC was elevated in non-diabetics with stroke compared to the control group was highly significant $P < 0.001$.

A study on lipid profile in non-diabetics with stroke done by Sridharan,[1] in 2010, showed a definite increase in serum TC in non-diabetic stroke patients when compared to control groups. In his study, he showed that both ischemic and hemorrhagic strokes are associated with increased cholesterol levels.

Benfante *et al.* (stroke 1994) showed that elevated serum cholesterol is a risk factor for both coronary heart disease and thromboembolic stroke in Hawaiian Japanese men.

Mascio *et al.* showed a positive association between risk of stroke and serum cholesterol.

Iso *et al.* emphasized an inverse association between serum cholesterol level and hemorrhagic stroke, but in his study, there was a positive association with non-hemorrhagic stroke.

Tanizaki *et al.* had showed that TC was an addition risk factor for cardioembolic stroke in females.

Strorn *et al.*, in 1994, showed that low TC levels decrease stroke in coronary artery disease patient.

Mohankar *et al.*, 1993, observed that increase TC leads to increase the incidence of atherosclerosis of large vessels. Atherosclerosis is a definite risk factor for stroke.

Triglycerides Association with Non-diabetic Stroke

The serum triglycerides were high in our patients compared to the control group of our study showing statistical significance ($P < 0.05$).

Sridharan[1] in his study showed that 80% of non-diabetic stroke patients with serum triglyceride >200 mg/dl had ischemic stroke and the remaining 20% had hemorrhagic stroke.

Tilvis *et al.*,[2] in his study, had showed that serum triglyceride is higher in ischemic stroke. Farid *et al.* also had similar results in his study in 1972.

Albucher *et al.*,[3] 2000, have showed serum triglycerides in normal range in his study on stroke.

Hachinski *et al.* showed a positive association of triglycerides in patients of atherothrombotic stroke and transient ischemic attacks.

Association of Serum HDL Cholesterol

The levels of serum HDL cholesterol are not significant in this study conducted on 60 non-diabetic stroke patients.

Simons *et al.* study revealed that HDL cholesterol had protective effect on ischemic stroke.

The northern Manhattan study on stroke in 2001 concluded that higher values of HDL cholesterol were associated with reduced risk of stroke.

Mohankar *et al.*,[4] in 1993, showed that increased LDL levels and low HDL levels were associated with atherosclerosis.

Mithee *et al.* had shown that high HDL levels were associated with decreased non-fatal stroke risk.

A study by Rubens *et al.*, in 2001, showed Gemfibrozil which raises HDL cholesterol level decrease ischemic stroke by 31% in men.

Albucher *et al.*[3] study clearly indicated HDL cholesterol as the only lipid associated with stroke risk. He emphasized the need for the management of low HDL cholesterol in young patients regardless of atherosclerosis.

Association of Serum LDL Cholesterol

The levels of serum LDL cholesterol were highly significant in our study conducted on 60 non-diabetics with stroke ($P < 0.001$).

Sridharan[1] showed that raised levels of serum LDL cholesterol had significant risk of ischemic stroke in non-diabetics.

Bolet *et al.* and Hachinski *et al.*[5] have showed positive correlation between LDL cholesterol levels and risk of stroke.

Ansell,[6] in 2000, showed that patients with established atherosclerosis showed are treated with statins to lower LDL cholesterol levels <100 mg to decrease the incidence of stroke.

Kurth *et al.*,[7] 2007, showed remarkable increase in serum LDL levels in ischemic stroke patients.

VLDL

VLDL levels were significantly elevated in our study conducted on 60 non-diabetics with stroke and control group.

Bidyadhar *et al.*,[8] 1984, showed that VLDL was raised in their study on stroke.

Sridharan,[1] in his study, showed that high VLDL was not associated with risk of stroke in non-diabetic patients.

CONCLUSION

Our study was conducted on 60 non-diabetic stroke patients and 60 controls. Exclusion was done because diabetes is associated with hyperlipidemia and atherosclerosis.

This study showed a significant association of TC, triglycerides, and LDL cholesterol in non-diabetics with stroke. High levels of TC, triglycerides, and LDL cholesterol are associated with higher risk of stroke.

Lowered HDL cholesterol levels were not significantly associated with stroke. The ratio of HDL/LDL cholesterol and TG/HDL cholesterol was calculated.

Dyslipidemia is a tip in iceberg. Dyslipidemia if properly treated being a modifiable risk factor for stroke it decreasing the incidence of stroke due to dyslipidemia. This leads to decrease morbidity and mortality, leading to a healthier society.

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Original Article

Evaluation of Thyroid Dysfunction in Abnormal Uterine Bleeding with Ovarian Dysfunction (AUB-O)

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Abstract

Introduction: Abnormal uterine bleeding with ovarian dysfunction (AUB-O) is one of the most frequently encountered conditions in gynecology and defined as an abnormal bleeding from the uterus in the absence of organic disease of genital tract and demonstrable extragenital cause.

Aims and Objectives: The objectives of the study were to study the menstrual pattern in patients with thyroid dysfunction and to study the thyroid dysfunction from puberty to premenopausal age group in AUB-O.

Results: AUB-O is one of the most frequently encountered conditions in gynecological practice which will give a descriptive analysis of the age distribution, the parity distribution, symptomatic distribution of AUB-O, and its association with thyroid dysfunction.

Conclusion: Our study concludes that thyroid dysfunction should be considered as an important etiological factor for menstrual abnormality. Thus, biochemical evaluation of T3, T4, and thyroid-stimulating hormone estimations should be made mandatory in AUB-O cases to detect apparent and occult thyroid dysfunction.

Key words: Abnormal uterine bleeding with ovarian dysfunction, Hyperthyroidism, Hypothyroidism

INTRODUCTION

Abnormal uterine bleeding with ovarian dysfunction (AUB-O) is one of the most frequently encountered conditions in gynecology and defined as an abnormal bleeding from the uterus in the absence of organic disease of genital tract and demonstrable extragenital cause.[1]

Regular cyclic menstruation results from the choreographed relationship between the endometrium and its regulating factors, changes in either of these frequently result in abnormal bleeding.[2] AUB-O affects 20–30% of women[3] and accounts for 12% of the gynecological-related complaints.[4] Thyroid hormones play an important role in normal reproductive function, both through direct effects on the ovaries and indirectly by interacting with sex hormone-binding protein.[5]

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It is recognized universally that menstrual disturbances may accompany clinical alterations in thyroid function, and every clinician has encountered altered menstrual patterns among women suffering from hypothyroidism and hyperthyroidism.[6]

Diseases of thyroid gland are among the most prevalent disorders worldwide second only to diabetes.[7] Both hypo- and hyperthyroidism are associated with a variety of changes in reproductive function including delayed onset of puberty, anovulatory cycles, and abnormally high fetal wastage.[8]

Although the occurrence of menstrual disturbances in hypothyroid woman has been documented, the number of hypothyroid patients originally requiring treatment for menorrhagia has not been carefully elicited.[9]

Danese *et al.* recommended that hypothyroidism is frequent enough to warrant consideration in most older woman, justifying screening even in asymptomatic older women.

The introduction of serum thyroxine and serum thyroid-stimulating hormone (TSH) radioimmunoassay has increased the sensitivity and specificity of thyroid function testing. The serum TSH assay has been shown to be a

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sensitive indicator of diminished thyroid functional reserve since TSH levels become elevated before circulating serum thyroxine levels fall below the normal range.

Hence, this study is to evaluate the thyroid dysfunction in patients having abnormal menstrual bleeding from puberty to premenopausal age groups which will be justifiable and will help in further management of AUB-O.

Aims and Objectives

The objectives of the study were as follows:

1. To study the menstrual pattern in patients with thyroid dysfunction
2. To study the thyroid dysfunction from puberty to premenopausal age group in AUB-O.

MATERIALS AND METHODS

The present study aimed to establish the role of thyroid dysfunctions in relation to menstrual disturbances.

This study was carried out in the Department of Obstetrics and Gynaecology in Chanda Kantha Maternity Hospital, Warangal. One hundred women who were given clinically the diagnosis as AUB-O during the period from June 2018 to May 2019 were selected for the study.

Criteria for the Selection of Cases

1. All cases diagnosed to have AUB-O from puberty to premenopausal age groups
2. All patients had major complaint of menstrual disturbances, for example, menorrhagia, polymenorrhea, polymenorrhagia, metropathia hemorrhagica, metrorrhagia, oligomenorrhea, and hypomenorrhea
3. Patients who were on drug or hormones, intrauterine contraceptive device (IUCD) users, with overt clinical symptoms of thyroid dysfunction, and history of bleeding disorder were excluded from the study.

Method

- A detailed history was obtained with special relevance to age, bleeding pattern
- Onset, duration, amount of bleeding, and complaints related to thyroid dysfunction were noted in detail
- A thorough clinical examination including general physical examination, neck examination, gynecological, and systemic examination was carried out, with special reference to thyroid dysfunction; a clinical diagnosis of AUB-O was attained
- Patients with pre-existing thyroid disorders were excluded from the study
- All these patients were subjected to routine investigations such as hemoglobin percentage, blood counts, urine examination for albumin, sugar, microscopy, bleeding time, and clotting time (to rule out coagulation defect)
- Then, all patients were subjected for T3, T4, and TSH estimation in their sera.

T3, T4, and TSH were assayed by enzyme-linked immunosorbent assay method.

These tests were done in random blood samples as the variation in TSH secretion due to circadian rhythm with a peak at 01:00 h and nadir at 11:00 h is small and does not influence the timing of blood sampling.

The following were noted.

- Level of T3
- Level of T4
- Level of TSH.

Patients were then grouped into four categories:

- Euthyroid
- Subclinical hypothyroid
- Hypothyroid
- Hyperthyroid.

Patients found to have thyroid dysfunction were further managed with the help of physician.

RESULTS

AUB-O is one of the most frequently encountered conditions in gynecological practice.

The following few pages, there are tables which will give a descriptive analysis of the age distribution, the parity distribution, symptomatic distribution of AUB-O, and its association with thyroid dysfunction.

The total number of patients studied was 100 from June 2018 to May 2019.

According to Table 1, maximum number of patients in the study group belongs to the age group of 31–40 years – 37%. Between the age group of 41 and 50 years, 9 cases were seen (9%).

Table 1: Distribution of patients according to age

Age group (years)	Number of cases	Percentage
<20	25	25
21–30	29	29
31–40	37	37
41–50	9	9
Total	100	100

The above column shows relationship of AUB-O with parity. Among 100 cases of AUB-O, 22 patients were unmarried and nulliparas were 8. Eighteen patients were para 3. Nine patients were para 4. Two patients were para 5. In this study, maximum number of patients were para 2 (27%) and minimum number of patient presenting as clinical AUB-O cases were of para 5 [Table 2].

Table 3 shows the relationship of thyroid dysfunction to different age groups. Thyroid dysfunction was most common in the age group between 31 and 40 years – 47.82% followed with 26.08% among patients between 21 and 30 years. About 17.39% of patients of age group <20 years showed thyroid dysfunction.

Thyroid dysfunction was least common in patients age 41–50 years – 8.69%.

This shows that thyroid dysfunction becomes common in reproductive age group.

The difference in thyroid functioning in individual age groups is not statistically significant ($P = 0.65$ [NS], NS – not significant).

Table 2: Distribution of patients according to parity

Parity	Number of patients	Percentage
Unmarried	22	22
0	8	8
1	14	14
2	27	27
3	18	18
4	9	9
5	2	2
100	100	100

Table 4 shows how thyroid dysfunction which can be hypothyroidism, subclinical hypothyroidism, or hyperthyroidism is related to various types of bleeding abnormalities. Thyroid dysfunction was most common in patients with menorrhagia – 43.47% followed by metropathia hemorrhagica – 21.73% and in patients with oligomenorrhea – 17.39%.

Patients with polymenorrhagia had thyroid dysfunction in 8.69% of cases. Thyroid dysfunction was least common in patients with polymenorrhea (8.69%) and absent in patients with metrorrhagia and hypomenorrhea.

Patients who were hyperthyroid were exclusively presenting as oligomenorrhea. Subclinical hypothyroid and hypothyroid patients were presenting menorrhagia as their most common bleeding pattern.

The difference in thyroid functioning in individual type of AUB-O is not statistically significant ($P = 0.58$ [NS], NS – not significant).

Table 5 shows the relation of TSH levels to different types of bleeding patterns. Patients with TSH levels <0.5 all of them presented with symptoms of oligomenorrhea.

Patients with TSH levels moderately elevated 5.1 and above, as seen in subclinical hypothyroidism and hypothyroid, 47.61% of patients presented with menorrhagia, 9.52% of patients presented with polymenorrhea, polymenorrhagia, and oligomenorrhea each, and 23.8% presented with metropathia hemorrhagica. In this group, maximum number of patients presented with menorrhagia. Hence, in this table, it is seen that oligomenorrhea was seen in patients

Table 3: Thyroid dysfunction in different age groups

Age	Number of cases	Euthyroid	Hypothyroid	Sub-hypothyroid	Hyperthyroid	Total thyroid dysfunction	Percentage
<20	25	21	2	2	0	4	17.39
21–30	29	23	3	3	0	6	26.08
31–40	37	26	4	5	2	11	47.82
41–50	9	7	2	0	0	2	8.69
Total	100	77	11	10	2	23	

Table 4: Bleeding pattern and thyroid dysfunction

Types of bleeding	Number of cases	Euthyroid	Hypothyroid	Sub-hypothyroid	Hyperthyroid	Total TDF	Percentage
Metropathia	13	8	3	2	0	5	21.73
Hypomenorrhea	5	5	0	0	0	0	0
Menorrhagia	34	24	5	5	0	10	43.47
Metrorrhagia	5	5	0	0	0	0	0
Oligomenorrhea	20	16	2	0	2	4	17.39
Polymenorrhagia	11	9	1	1	0	2	8.69
Polymenorrhea	12	10	0	2	0	2	8.69
Total	100	77	11	10	2	23	

TDF: Testis-determining factor

Table 5: TSH levels and different bleeding patterns

TSH level	Number of cases	Metropathia hemorrhagica		Hypomenorrhea		Menorrhagia		Metrorrhagia		Oligomenorrhea		Polymenorrhagia		Polymenorrhea	
<0.5	2	0	-	-	-	-	-	-	-	2	100%	-	-	-	-
0.5–5 (normal range)	77	8	-	5	-	24	-	5	-	16	-	9	-	10	-
5.1 and above	21	5	23.8%	0	0	10	47.61%	0	0	2	9.52%	2	9.52%	2	9.52%

TSH: Thyroid-stimulating hormone

with TSH value <0.5. On the other hand, menorrhagia was mostly seen in patients with TSH value (5.1 and above) moderately elevated.

TSH normal range is 0.5–5 IU/ml.

Table 6 shows the relationship of T3 levels to different types of bleeding pattern. Patients with T3 levels <0.5 had metropathia hemorrhagica and menorrhagia in 27.27% of the patients. About 18.18% of patients had oligomenorrhea and polymenorrhea.

Where the T3 levels >1.85, all patients had oligomenorrhea.

Only 13% of the total number of patients showed abnormal T3 levels compared to 23% of patients who showed abnormal TSH levels.

T3 normal range is 0.52–1.85 ng/dl.

Table 7 shows relationship of T4 levels to different types of bleeding pattern.

Patients with T4 level <4.5, menorrhagia (40%) was present predominantly followed by metropathia hemorrhagica and oligomenorrhea (20%) each.

Patients with T4 levels >12 had predominantly oligomenorrhea as their complaints (100%).

Only 11% of the total number of patients showed abnormal T4 levels compared to 23% of patients who showed abnormal TSH levels.

T4 normal range is 4.5–11.6 μg/dl.

DISCUSSION

Thyroid dysfunction is marked by large number of menstrual aberrations. In the present study, patients were taken from all age groups which included <20 years, 21–30 years, 31–40 years, and 41–50 years and maximum number of patients were in the age group of 31–40 years. In a study by Doifode *et al.*, also maximum number of patients were in the age group of 31–40 years.

In the present study, patients with clinical signs and symptoms of thyroid dysfunction were excluded, but in author's study, all patients with menstrual aberrations irrespective of the presence of signs and symptoms of thyroid dysfunction were included in the study.

Patients with organic lesions of genital tract, drug (hormone) intake, bleeding disorders, and IUCD users

were excluded from the present study and also from the author's study (Difode, Fernandes).

The present study groups ranged patients according to parity as unmarried, nullipara, para 1, para 2, para 3, para 4, para 5, and above. Similarly, the author's study had also grouped parity into unmarried, nullipara, para 1, para 2, para 3, para 4, and more.

Table 8 compares the relationship of parity with thyroid dysfunction among patients with AUB-O (diagnosed clinically) in the present study and in the author's study.

In the present study, 17.39% of unmarried patients had thyroid dysfunction and in Doifode *et al.* study (2001), 15% of unmarried patients had thyroid dysfunction. In the present study, thyroid dysfunction was 4.34% among nulliparous patients as compared to the author's study which showed 6.67%. In the present study, patients with para 1, only 17.39% of them had thyroid dysfunction, but in the author's study, thyroid dysfunction was present in 33.33% of patients with para 1.

Maximum number of patients with thyroid dysfunction were para 2 (39.13%) in the present study as compared to the author's study, where maximum number of patients with thyroid dysfunction belonged to para 1.

Thyroid dysfunction was most common in the age group (31–40 years), both in the present study and also in the author's study. About 17.39% of patients with thyroid dysfunction were from the group of patients with AUB-O who were <20 years in the present study as compared to only 11.67% of patients with thyroid dysfunction were from this group. In a study (Doifode *et al.*), 23.33% of patients with thyroid dysfunction belonged to the age group of above 40 years in the author's study as compared to 8.64% of patients with thyroid dysfunction belonged to this age group (above 40) in the present study.

In the present study, 100 cases were taken with the complaint of abnormal menstruation. Cases of metropathia hemorrhagica, menorrhagia, polymenorrhagia, polymenorrhea, metrorrhagia, oligomenorrhea, and hypomenorrhea were included in this study.

In the author's study, 213 cases of clinically diagnosed AUB-O were taken. Patients with oligomenorrhea, hypomenorrhea, and polymenorrhea were excluded in the author's study. In both the studies, the most common complaint was menorrhagia.

In the study (Doifode *et al.*), 60 patients out of 213 patients showed their thyroid dysfunction as hypothyroidism (either subclinical or profound), the author's study had no case of hyperthyroidism.

Table 6: T3 levels and different bleeding patterns

T3 level	Number of cases	Metropathia	Hypomenorrhea	Menorrhagia	Metrorrhagia	Oligomenorrhea	Polymenorrhagia	Polymenorrhea
<0.5	11	3	0	3	0	2	1	2
0.5–1.85	87	10	5	29	5	16	10	12
>1.85	2	0	0	0	0	2	0	0

Table 7: T4 levels and different types of bleeding patterns

T4 levels	Number of cases	Metropathia	Hypomenorrhea	Menorrhagia	Metrorrhagia	Oligomenorrhea	Polymenorrhagia	Polymenorrhea
<4.5	10	2	0	4	0	2	1	1
4.6–12 (normal range)	89	11	5	28	5	17	10	13
>12	1	0	0	0	0	1	0	0

Table 8: Thyroid dysfunction in relation to parity

Para	Present study		Author's study Doifode *et al.*[29]	
	Number of patients with TDF	Percentage	Number of patients with TDF	Percentage
Unmarried	4	17.39	9	15
0	1	4.34	4	6.67
1	4	17.39	20	33.33
2	9	39.13	9	15
3	4	17.39	12	20
4 and above	1	4.34	6	10

TDF: Testis-determining factor

Even in the present study, 23 patients out of 100 patients showed thyroid dysfunction. Twenty-one patients were hypothyroid either subclinical or profound and two patients were hyperthyroid.

In the present study, 76.19% of patients were hypothyroid and 100% of patients were hyperthyroid in multipara.

In Sharma *et al.* study (2012), 81.81% of patients were hypothyroid and 85.71% were hyperthyroid in multipara.

In Sharma *et al.* study, 64% of patients were euthyroid, 22% of patients were hypothyroid, and 14% were hyperthyroid.

In Kour *et al.* study, 85% of patients were euthyroid, 14% were hypothyroid, and 1% of patients were hyperthyroid.

In the author's study, patients with clinical signs and symptoms of hypothyroidism were also included in the study, whereas in the present study, patient with clinically diagnosed AUB-O with any signs or symptoms of hypothyroidism were excluded from the study.

In the present study, hypothyroidism was the most common (i.e., 21%) thyroid dysfunction seen in patient with all the seven different types of menstrual disturbances.

The type of menstrual abnormality commonly seen in hypothyroidism was menorrhagia (63.33%) in the author's study. Menorrhagia was the most common menstrual abnormality even in the present study, i.e., 47.61%. Polymenorrhagia was the next common menstrual abnormality, i.e., 23.33% in the author's study. Metropathia hemorrhagica was the next common menstrual abnormality, i.e., 23.8% in the present study.

The author's study had excluded cases of polymenorrhea. In the present study, polymenorrhea was present in 9.52% of hypothyroid cases.

The author had excluded cases of oligomenorrhea. In the present study, oligomenorrhea was the menstrual pattern in 9.52% of hypothyroid patient.

In Kour *et al.* study, oligomenorrhea was present in 21.4% of hypothyroid patients.

Subclinical hypothyroidism is diagnosed in cases with normal levels of T3 and T4 (low normal levels) and raised TSH levels. In the table below, cases with menorrhagia who were having subclinical hypothyroidism in the present study were compared with the author's study (Douglas *et al.*, 1989).

Subclinical hypothyroidism was seen in 22.3% of cases with menorrhagia in the author's study (Douglas *et al.*, 1989).

Similarly, in the present study, subclinical hypothyroidism was seen in 23.8% of cases with menorrhagia. The incidence of subclinical hypothyroidism was similar in the present study and in the author's study (Douglas *et al.*, 1989).

In the present study, 9 cases of menorrhagia in the age group of <20 years were studied, of which 1 case had hypothyroidism. In the author's study (Mukherji *et al.*, 1986), 70 cases of menorrhagia were studied <20 years, of which 5 patients were hypothyroid.

In the present study, hypothyroidism was seen in menorrhagia patients (<20 years) in 11% of cases. In the author's study, hypothyroidism was seen in 7.14% of menorrhagia patients <20 years.

In the present study, there were total 20 cases of oligomenorrhea, in which 6 cases were from patients <20 years, 8 cases were patients between 21 and 30 years, 5 cases were patients between 31 and 40 years, and 1 case was patient above 40 years.

In the author's study (Mukherjee *et al.*, 1985), 10 cases of oligomenorrhea were taken, age ranging between 25 and 39 years, mean age being 31.7 ± 2.8 years.

In the author's study, there were no cases among oligomenorrhea patients who had hyperthyroidism. In the present study, 10% of oligomenorrheic patients were showing hyperthyroidism and 10% were having hypothyroidism. Total patients show that thyroid dysfunction in the present study is 20% and in the author's study is 80%.

In the author's study, patients with oligomenorrhea and thyroid dysfunction showed 63.6% of hyperthyroidism and 36.3% of hypothyroidism.

In the present study, patients with oligomenorrhea and thyroid dysfunction showed 50% of hyperthyroid cases and 50% of hypothyroid cases. In the present study, hyperthyroidism was seen only in the cases of oligomenorrhea.

Hence, in both the present study and author's study (Singh *et al.*, 1990), oligomenorrhea was the most common menstrual aberration among hyperthyroid patients.

CONCLUSION

Our study concludes that thyroid dysfunction should be considered as an important etiological factor for menstrual abnormality.

Thus, biochemical evaluation of T3, T4, and TSH estimations should be made mandatory in AUB-O cases to detect apparent and occult thyroid dysfunction.

These patients with thyroid dysfunction if given medical treatment avoid necessity of hormonal treatment or surgical intervention.

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Original Article

Study of Factors Affecting the Outcome in Acute Kidney Injury (AKI)

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Abstract

Background: Acute kidney injury (AKI) continues to be associated with high mortality despite the significant improvement in medical care. Factors other than renal functions probably determine the outcome, and their identification is necessary to improve the prognosis.

Materials and Methods: This is a prospective clinical descriptive study done between March 2018 and April 2019. Fifty patients admitted to Mahatma Gandhi Memorial Hospital, Warangal, with AKI were included in the study. Every patient will be evaluated by detailed history, clinical examination, and relevant investigations.

Results: Oliguria or anuria, fever, and altered sensorium were the most common presenting symptoms. Medical causes top first among the causes of AKI in 80% followed by surgical 16% and obstetric 4%. Among the medical causes, acute gastroenteritis with septicemia 34%, severe malaria 20%, and pneumonia with septicemia 10% is the predominant cause. Among surgical causes, sepsis following trauma was the leading cause. Among 50 cases, 15 (30%) completely improved, 12 (24%) cases only partially improved, and 23 (46%) cases not improved and dead. Surgical causes of AKI had 75% mortality rates. Patients presented with oliguria, altered sensorium, jaundice, or coma, and patients with high mean blood urea and serum creatinine at admission had high mortality rates. Patients with multiorgan dysfunction syndrome, hyperkalemia, septic shock, hypertension, ischemic heart diseases, and diabetes mellitus had significantly poor outcome.

Conclusion: Many factors other than AKI determine the outcome in AKI. Early and prompt diagnosis and treatment of primary disease-causing AKI with prevention and aggressive treatment of complications can improve the mortality.

Key words: Acute kidney injury, Factors, Outcome

INTRODUCTION

The kidney is remarkable among organs of the body in its ability to recover from almost complete loss of function, and most acute kidney injury (AKI) is potentially reversible, though with subclinical residual defects in tubules and glomerular functions.[1] AKI is associated with major inpatient morbidity and mortality, reflecting the severity of the causal illness and the high frequency of complications.[2,3]

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AKI complicates nearly 5% of the hospital admissions and up to 30% of intensive care unit admissions.[3] In most of the cases, it is potentially, reversible if recognized early and managed appropriately at a right time.[4]

The etiology of AKI is closely linked to the prevailing socioeconomic and environmental conditions in a given geographic location. In India itself, there are differences in the etiology of AKI in different parts of the country. This is reflected as the difference in occurrence of etiology from studies conducted at different parts of the country.

There is a paucity of data from this area of the country about the incidence, clinical course, and the factors affecting the outcome in AKI.[5,6] This study is being taken to study the clinical course, the outcome, and the factors affecting the outcome in AKI in our set up.

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Aim of the Study

The aim of the study was as follows:

1. To study the clinical profile, course, and outcome of the patients presenting with AKI to Mahatma Gandhi Memorial Hospital, Warangal
2. To know the factors affecting the outcome in AKI presenting to our hospital.

MATERIALS AND METHODS

This is a prospective clinical descriptive study done between October 2005 and July 2007. Fifty patients of AKI admitted to Mahatma Gandhi Memorial Hospital, Warangal, were included in the study.

Case Selection

Clinical diagnosis of AKI was considered when an abrupt increase in serum creatinine and blood urea, with or without a decrease in urine output in a person with previously normal renal function.

Inclusion Criteria

Patients who satisfy any one of the following criteria were included in the study.

1. Patients with AKI clinically diagnose when serum creatinine increases to more than 2 mg/100 ml with or without oliguria [Table 1]
2. Patients with steady increase in serum creatinine concentration of at least 1 mg/100 ml over 48 h
3. Patients with an increase in serum creatinine by more than 20% per day if the baseline is more than 2.5 mg/100 ml [Table 2].

Exclusion Criteria

The following criteria were excluded from the study [Table 3]:

1. Patients aged <15 years
2. Patients with a history of severe chronic renal failure with usual serum creatinine concentration more than 3 mg/100 ml
3. Patients with previous renal transplantation
4. Patients with evidence of contracted kidneys on ultrasound scan abdomen.

Diagnostic Approach Followed

1. A detailed history and physical examination as per pro forma [Table 4]
2. Blood urea, serum creatinine, and serum electrolytes
3. Urine analysis
4. Complete hemogram, blood smear for malarial parasites [Table 5]
5. Blood for leptospiral antibody, dengue antibody, and rapid card test for malaria
6. Daily fluid intake output measurements
7. Ultrasound abdomen scan
8. Electrocardiography
9. If indicated, the following were done.
    - Urine for myoglobin, leptospira
    - Liver function test
    - Arterial blood gases analysis
    - Chest X-ray
    - Blood culture and sensitivity.

Patients were followed clinically and by serial biochemical tests and were started on conservative treatment, if indicated patients were taken for hemodialysis.

Statistical Methods

Chi-square test/2 × 2, 2 × 3, and 3 × 3 Fisher's exact test has been used to find the significant association of study characteristics with the outcome. About 90% confidence interval has been used to find the significance of study characteristics in the present study.

RESULTS AND OBSERVATION

Study Design

A prospective clinical descriptive study of 50 patients with AKI is undertaken to study the factors affecting the outcome.

About 34% of patients with AKI were between 20 and 40 years, 36% between 40 and 60 years, and 30% above 60 years. Mean age of incidence was 49.48 years.

Out of 50 patients, 35 were male and 15 were female, constituting 70% and 30%, respectively. Male and female ratio in this study is 2.33:1.

Among the various signs and symptoms at presentation, oliguria or anuria, fever, and altered sensorium were the most common followed by diarrhea, vomiting, and breathlessness. They can be either the features of the primary disease that caused AKI or the features of the complication of AKI.

Among the surgical causes of AKI, most patients presented with road traffic accidents, acute pain abdomen, vomiting, and fever.

Among the various comorbid conditions and risk factors studied in the present study, the most common is found to be due to multiorgan dysfunction followed by diabetes mellitus and ischemic heart disease.

The AKI cases with anuria, hyperkalemia, pulmonary edema, uremic encephalopathy, and multiorgan dysfunction were taken up for hemodialysis 24 (48%). The remaining 26 (52%) cases were treated conservatively and followed for improvement in renal functions.

Among 50 cases of AKI, 15 (30%) patients improved [Table 6], 12 (24%) patients only partially improved, and 23 (46%) patients not improved and died.

In the present study of AKI, patients who improved had prolonged hospital stay [Table 7]. Partially improved patients were started on maintenance hemodialysis and got discharged early with short hospital stay. Patients who did not improve and died early due to complications of AKI or of the primary disease so had shorter duration of hospital stay.

DISCUSSION

The observations made in 50 cases of AKI admitted to Mahatma Gandhi Memorial Hospital, Warangal. The study was done between March 2018 and April 2019.

The results are compared with other studies.

Age and Sex

In the present study, age of the patients ranged between 20 and 80 years with mean age of 49.48 years. There were 70% of males and 30% of females, with male-to-female ratio 2.33:1 [Table 8]. In the present study, the mean age was less compared to other studies.

They are comparable with other studies, as shown in the tabular column below.

Table 1: Age distribution

Age in years	Number	Percentage
20–30	10	20.0
31–40	7	14.0
41–50	12	24.0
51–60	6	12.0
61–70	10	20.0
>70	5	10.0
Total	50	100.0
Mean±standard deviation	49.48±17.58	

Table 2: Gender distribution

Gender	Number	Percentage
Male	35	70.0
Female	15	30.0
Total	50	100.0

Table 3: Presentation of signs and symptoms

Signs and symptoms	Number (*n*=50)	Percentage
Fever	26	52.0
Oliguria	20	40.0
Altered sensorium	19	38.0
Diarrhea	17	34.0
Vomiting	16	32.0
Breathlessness	16	32.0
Abdominal pain	11	22.0
Edema	10	20.0
Anuria	10	20.0
Cough	9	18.0
Jaundice	9	18.0
Coma	3	6.0

Symptoms and Signs of AKI

The study of common presenting symptoms and signs was made. We noted that oliguria and anuria, fever, and altered sensorium were the most common symptoms, followed by diarrhea, vomiting, and breathlessness.

The variations in the presenting symptoms and signs compared to other studies could be due to differences in causes and varying degrees of complications in different studies [Table 9].

Causes of AKI

In the present study, out of 50 cases of AKI medical causes topped the list comprising 80%, surgical causes 16%, and only 4% due to obstetric causes.

Among the medical causes, acute gastroenteritis (GE) 17 cases was the most common followed by severe malaria and pneumonia with septicemia [Table 10].

In the study by Sirwal *et al.* in the "Profile of AKI in Kashmir valley" which had 78.6% of cases due to medical causes, the leading cause was that due to acute GE accounting for 26.2% of cases compared to 34% in the present study.

Ramachandran in "AKI in Sri Lanka from Colombo," medical causes accounted for 74% of cases, of which the leading cause was that of snakebite.

In Kaufman *et al.* study in "Community-acquired AKI from Boston," among medical causes, acute GE was the leading cause in 25% of cases.

Table 4: Comorbid conditions of patients studied

Comorbid conditions	Number (*n*=50)	Percentage
Absent	27	54.0
Present	23	46.0
MODS	9	18.0
DM	7	14.0
IHD	4	8.0
HTN	2	4.0
CCF	1	2.0

Table 5: Treatment modalities for acute kidney injury

Treatment modalities	Number (*n*=50)	Percentage
Conservative	26	52.0
Hemodialysis	24	48.0

In the present study, severe malaria was the second most common cause of AKI accounting for 20% in that of falciparum malaria. This could be due to the endemicity of malaria in this area of study.

In the study by Singhal *et al.*, malaria was the predominant cause of AKI involving about 16% of cases with falciparum in 80% of patients.

In the study by Prakash *et al.*, 15% of patients had AKI due to malaria, with falciparum malaria responsible for 76%. These are comparable to the present study.

Table 6: Outcome in patients studied

Outcome	Number (*n*=50)	Percentage	90% Confidence interval
Improved	15	30.0	20.59–44.46
Partially improved	12	24.0	15.57–35.10
Not improved and death	23	46.0	34.91–57.50

Table 7: Association of the length of hospital stay with outcome

Outcome	Length of hospital stay	
	Range	Mean±standard deviation
Improved	4–31	11.67±8.79
Partially improved	1–21	12.00±5.43
Not improved and death	1–15	6.30±3.89
Significance		F=5.103, *P*=0.010*

Significant Value is *P*=0.010

Table 8: Comparison with few other studies

Study series	Males in %	Females in %	Mean age group (years)
Present study	70	30	49.48
Bernieh *et al.*	58	36	56.2
Singhal *et al.*	63	34	53.5

In the present study, septicemia due to various etiologies was responsible for AKI in 56% of total AKI cases. This is comparable to the study done by Bernieh *et al.*, who found septicemia causing AKI in 58% of cases.

Surgical cause of AKI found in 16% of patients in the present study, which is comparable to 9.8% of cases due to surgical AKI in Muthusethapathi *et al.* in their "Study AKI in Madras."

In the present study, drug-induced nephropathy was seen in 2 (4%) of cases, which is comparable to the study by Bernieh *et al.*, who found drug-induced nephropathy in 6% of cases of AKI. Singhal *et al.* reported drug-induced AKI in 3% of patients.

In the present study, snakebite with cellulitis induced AKI in 2 (4%) of eases which is comparable to 4% of the Chug *et al.* study from Chandigarh.

Outcome and Factors Affecting Outcome

The outcome of AKI studied:

In the present study, out of 50 cases of AKI, 15 (30%) completely improved, 12 (24%) only partially improved, and 23 (46%) not improved and dead.

This is comparable to the study done by Mahakur *et al.* who had 44% of mortality in AKI.

This is in contrast to the study done by Mathur *et al.* who found that 71% of AKI cases recovered completely, 9% only partially improved, and 20% not improved and dead.

The course of stay in hospital and outcome of these patients with AKI is variable. In the present study, improved patients had longer duration of stay 4–31 days, compared to 1–15 days for dead. Duration of hospital stay is generally longer for hospital survivors.

Table 9: Comparative studies showing symptoms and signs

Symptoms and signs	Present study %	Bernieh *et al.* %	Singhal *et al.* %	Liano *et al.* %
Oliguria and anuria	60	78	80	80
Fever	52	-	68	-
Altered sensorium	38	-	-	-
Diarrhea	34	-	-	-
Vomiting	32	80	85.2	86
Breathlessness	32	-	-	-
Edema	20	20	-	-
Jaundice	18	-	20	-

Table 10: Findings with comparable to other studies

Major causes	Present study	Chug *et al.*	Muthu Sethapathi *et al.*	James Kaufman *et al.*	Sirwal *et al.*	Rama Chandran
Medical	80	61	81.2	83	78.6	74
Surgical	16	30	9.8	17	14.3	15
Obstetric	4	9	9	0	7	6

Association of Symptoms and Outcome

In the present study, AKI patients who presented with altered sensorium, coma, jaundice, or oliguria had higher mortality. This is comparable to the study done by Chew *et al.* in their study of "Outcome in AKI."

Causes of AKI with Outcome

In the present study, AKI due to various causes associates with septicemia and septic shock had high mortality. Out of 25 AKI cases due to sepsis-associated causes, 15 (60%) cases died. These finding are comparable to the study done by Nevu *et al.*, who found mortality of 74.5%.

In the present study, the mortality rate for severe malaria is 76% which is comparable to the study "Malaria in AKI" done by Mahakur *et al.* who found mortality in 44% of AKI cases due to malaria.

Among the surgical causes of AKI, mortality was seen in 75% of cases in the present study which is comparable to various outcome studies.

In the present study, out of 30 cases, oliguric and anuric AKI had an overall poor outcome with 9 (33%) cases partially improved and 16 (50%) patients not improved and dead. This is comparable to the study by Anderson *et al.* in "Non-oliguric AKI" who found the similar outcome, which is also comparable to a study done by Susan *et al.* in "Hospital-acquired renal insufficiency."

In the present study, magnitude of the increase in serum creatinine levels showed a significant mortality which is comparable to the study done by Hou *et al.*, who found the similar outcome.

In the present study, the patients with comorbid conditions are 3 times more likely to have death compared to their absence. This also observed in the outcome study, done by Chew *et al.* in his study "outcome in AKI."

The study done by Prakash *et al.* also showed that prognosis in AKI is grave when multiple comorbid conditions are present.

One case of HS syndrome following acute GE only partially improved and is on maintenance hemodialysis. This is comparable to the study done by Dedhia *et al.*

Treatment Modality on Outcome

In the present study, out of 50 cases of AKI, 26 (52%) cases were treated conservatively and 24 (48%) underwent hemodialysis. Patients treated conservatively significantly improved with survival rates 67.5% than those treated with hemodialysis. Among 24 cases who underwent hemodialysis, 50 cases not and died. This may be due to the severity of AKI itself or due to its complications requiring hemodialysis. This is comparable to the study by Nevu *et al.*, who found that mortality was higher in dialyzed than non-dialyzed AKI cases. This is also comparable to Hakim *et al.*, in their study, about 58% of patients survived with conservative treatment of 48% of patients survived with hemodialysis.

The major risk factors affecting the prognosis were the severity of primary disease, the presence of multiorgan dysfunction, high baseline urea and creatinine levels, and other associated comorbid conditions.

CONCLUSION

- AKI is potentially a reversible condition
- Mean age of presentation 49 years
- Medical causes accounted for 80% of cases with acute GE, severe malaria and pneumonia were the leading causes of AKI
- Clinical features observed were almost comparable to studies conducted earlier
- Oliguria and anuria present in 60% of cases
- About 30% of AKI cases improved completely, 24% of cases partially improved, and 46% of cases were not improved and dead
- About 52% of cases were treated conservatively and 48% of cases required hemodialysis
- Factors such as septicemia, septic shock, surgical causes of AKI, presence of comorbid conditions, and complications were associated with adverse outcome.

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Original Article

Arterial Blood Gas as a Prognostic Tool in Organophosphorus Poisoning Patients – A Prospective Observational Study

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Abstract

Introduction: Organophosphorus (OP) compounds constitute a heterogeneous category of chemicals specifically designed for the control of pests, weeds, or plant diseases. Intentional ingestion of OP pesticides has been common and now the preferred form of poisoning due to its easy access in central and Southern parts of India. This predominantly occurs in rural communities. As a result of widespread use, OP poisoning is a major cause of morbidity and mortality worldwide.

Aim: This study aims to access the arterial blood gas (ABG) analysis as a prognostic prediction tool in OP poisoning patients.

Materials and Methods: This is a prospective study from February 2017 to March 2018, out of 114 patients who presented to the emergency department, 14 patients were excluded from the study and the remaining 100 patients were included in the study.

Results: Males were the most predominant group in OP ingestions in this study. In 29% of patients, the ABG interpretation was normal and metabolic acidosis in the initial ABG had a mean intensive care unit (ICU) stay value of 12.92; respiratory acidosis had a mean ICU stay value of 12.36; mixed acidosis had a mean ICU stay value of 9.33; respiratory alkalosis had a mean ICU stay value of 5.37; metabolic alkalosis had a mean ICU stay value of 4.66. *P*-value was calculated and found to be statistically significant. Moreover, it was also found that the patients who presented with extreme acidosis (≤7.1) had increased mean ICU stay value (17.5).

Conclusion: This study concludes that ABG analysis at the initial presentation could help in assessing the prognosis of OP poisoning patients much earlier, which could help in intensifying the management.

Key words: Arterial blood gas analysis, Organophosphorus, Poisoning

INTRODUCTION

Pesticides include a wide variety of compounds which include insecticides, herbicides, fungicides, and others. Thus, far more than 1000 active substances have been determined in approximately 35,000 preparations of pesticides used in agriculture.[1] Organophosphorus (OP) pesticide poisoning is a serious hazard. OP compounds (OPC) poisoning is an important clinical problem in the rural regions of the developing countries.[2] The adult mortality rate due to OP poisoning in rural South India is 0.97/1000 persons/year.[3] Around 200,000 people around the world die each year from OPC poisoning, especially in developing countries.[4] OP groups of poison exist since the 19th century.[2] The first OPC was developed as an insecticide for agriculture and now different varieties of OP pesticides are available in the market each having different toxicity levels.[2] Acute OP pesticide poisoning is common in developing countries due to easy availability and less awareness among poorly educated farmers. Hence, farmers are at high risk for accidental exposure to OPC poisoning. However, poisoning with suicidal intent is more common than accidental exposure.[5] Intentional ingestion of OP pesticides has been common for the past 40 years. A fatal outcome is often related to delay in diagnosis or improper management. This predominantly occurs in rural

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communities and is often an impulsive act comparable to self-poisoning with medication in the west; the critical difference is 10–20% of case fatality rate (compared to 0.3% in Britain).[4]

OPCs are available as dust, granules, or liquids. OPCs are very well absorbed from the lungs, gastrointestinal tract, skin, mucous membranes, and conjunctiva following inhalation, ingestion, or topical contact. Most OPCs are lipophilic. Peak levels of most OP insecticides measure around 6 h after oral ingestion in man.[6,7]

OP pesticide inhibits both cholinesterase and pseudocholinesterase activities; as a result, there is an accumulation of acetylcholinesterase at synapses causing overstimulation and disruption of neurotransmission in both central and peripheral nervous systems. Although organophosphates differ structurally from acetylcholine, they can bind to acetylcholinesterase molecule at the active site and phosphorylate the serine moiety. When this occurs, the resultant conjugate is infinitely more stable than the acetylcholine-acetylcholinesterase conjugate although endogenous hydrolysis does occur. The rate of onset of clinical features will vary between people and between OPCs but is mostly within minutes to hours depending on the dose. Some OP insecticides can cause delayed onset of severe poisoning after a day or 2 days. Directly acting OP insecticides can inhibit acetylcholinesterase without being structurally altered. However, many OPCs, such as parathion and malathion, are indirect inhibitors requiring partial metabolism within the body to become active.[8]

Exposure to OP vapors rapidly causes upper airway irritation and bronchospasm followed by systemic symptoms. Acute respiratory failure is the most common cause of death in OPC poisoning due to increased secretions and inadequate ventilation. One of the causes of complications is an acid-base imbalance. Subsequent measures must be carried out by recognizing and correcting the acid-base disturbance at the earliest possible time.[9,10]

Evaluation of acid-base status in the OPC poisoning patients plays a critical role as early recognition of acid-base disturbance can alter the management and prognosis. Moreover, it is also very essential to determine the respiratory failure following which endotracheal intubation and, mechanical ventilation can be done.

Aim

This study aims to access the arterial blood gas (ABG) analysis as a prognostic prediction tool in OP poisoning patients.

MATERIALS AND METHODS

This is a prospective study from February 2017 to March 2018 where a specific set of data was collected from the patients who fulfilled the inclusion criteria. A total of 114 patients were enrolled, of which 14 were excluded from the study and the remaining 100 patients accounted.

Inclusion Criteria

The following criteria were included in the study:

- Age of more than 18
- Clinical features suggestive of OP poisoning
- Written and informed consent (in the local language)
- Consumption of OPC as per.

Patient, relatives, referring doctor, and the pesticide container.

Exclusion Criteria

The following czriteria were excluded from the study:

- Any mixed ingestions
- Age <18
- Time of consumption more than 24 h
- Discharge against medical advice (no follow-up)
- Other forms of OP poisoning other than oral ingestion, for example, inhalation
- Comorbidities such as chronic kidney disease, chronic obstructive pulmonary disease, congestive heart failure, and chronic lung disease.

The acid-base status being the priority, data were collected at the initial presentation of the OP poisoning. Arterial blood collected from the radial artery and femoral artery. The radial artery at the wrist was the most preferred site of ABG specimen collection as it has adequate collaterals. When this was not feasible, femoral artery was chosen to collect the sample. Estimation was done using the ABG analyzer. The results of the ABG were recorded and analyzed. Then, according to the report, acid-base status determined. Data were collected by the study doctor, wherein during the examination, initial resuscitation was carried out. Initial resuscitation was done in emergency department (ED) and further treatment was subjected to the intensive care unit (ICU) physician.

The treating critical care physician was not notified of the study and was blinded so as to avoid any bias in assessing the ICU stay in the selected group of patients.

The acid-base status being the priority, data were collected at the initial presentation of the OP poisoning.

RESULTS

Most numbers of patients who consumed OPCs were found to be between 20 and 40 years which were 69 in number. The next significant group was 40–50 years old which had 15 patients Figure 1. Males were the more predominant group in OP ingestions in this study. Most of the patients consumed monocrotopos and chloropyripos compounds [Figure 2]. Most cases presented within 1 h-4 h of ingestion, which was 53 in number. 25 cases presented within 30 to 60 min of ingestion and 15 cases presented within 30 min of ingestion [Table 1 and Figure 3].

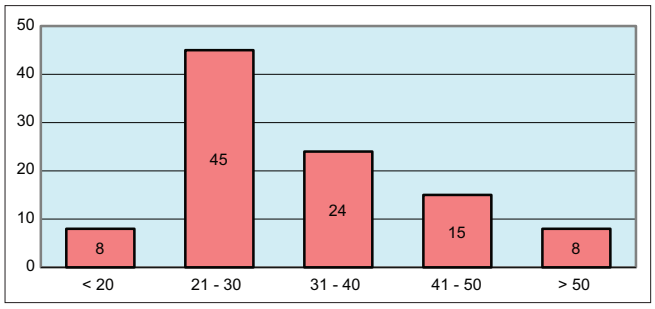

Figure 1: Age distribution

Out of 24 cases who are initial ABG showed metabolic acidosis, 3 deaths were reported. Out of 11 cases, who initially presented with respiratory acidosis, 2 deaths were reported; and out of 3 cases, 1 death was reported. In cases who presented with respiratory and metabolic alkalosis, no deaths were reported. Out of 100 cases, 42 cases required invasive ventilation. Out of 100 patients, 94 patients recovered and death reported in 6 patients. Patients with pH <7.10 had a mean ICU stay value of 17.5; patients with pH ranging from 7.11 to 7.20 had a mean ICU stay value of 12.1; patients with a pH ranging from 7.21 to 7.35 had a mean ICU stay value of 11.23. The mean ICU stay of patients presenting with pH of 7.45–7.49 is 5.6; and patients presenting with pH >7.50 had a mean ICU

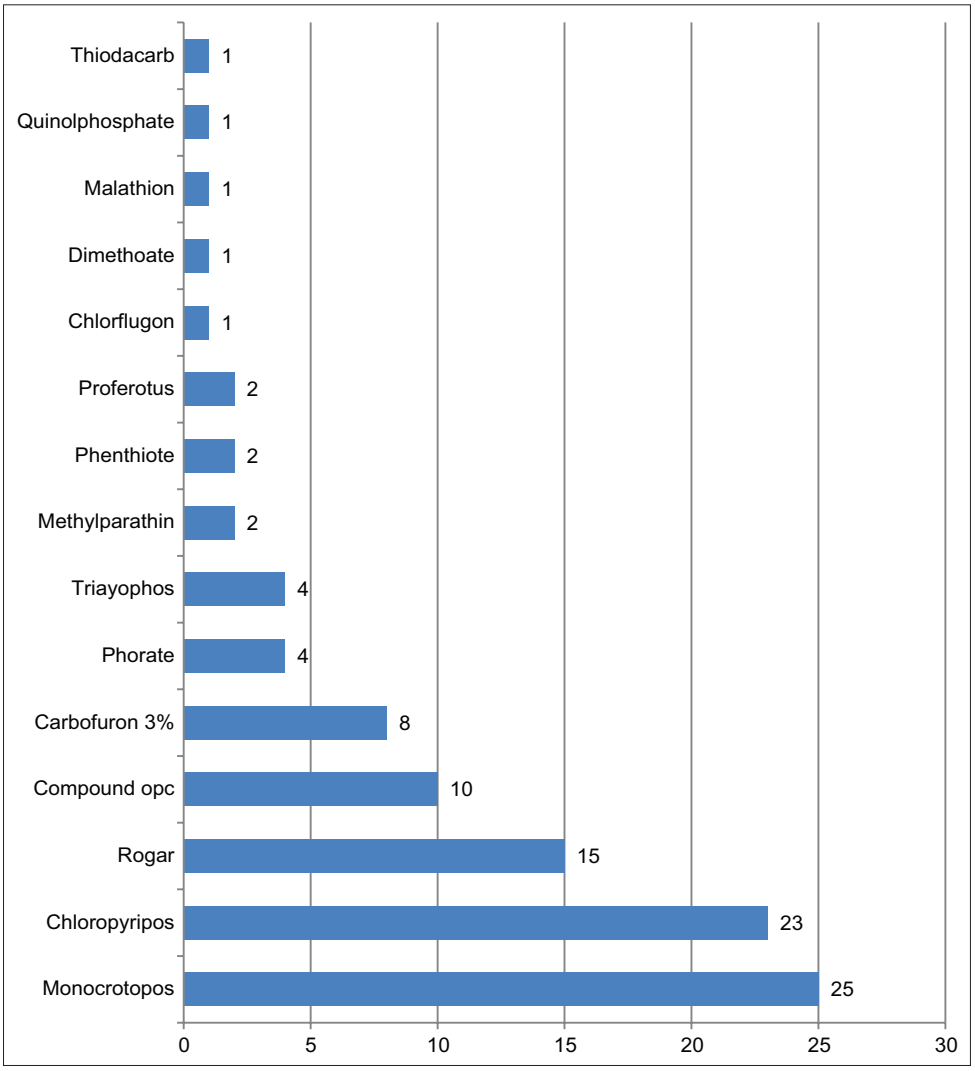

Figure 2: Organophosphorus compounds

Table 1: Comparison ABG analysis and ICU stay

Comparison	Mean	Standard deviation	*P*-value
Metabolic acidosis (24) versus metabolic alkalosis (3)	12.92	3.92	0.001
	4.67	0.58	
Metabolic acidosis (24) versus respiratory acidosis (11)	12.92	3.92	0.684
	12.36	3.11	
Metabolic acidosis (24) versus respiratory alkalosis (30)	12.92	3.92	<0.001
	5.37	2.54	
Metabolic acidosis (24) versus mixed acidosis (3)	12.92	3.92	0.137
	9.33	2.08	
Metabolic acidosis (24) versus normal (29)	12.92	3.92	<0.001
	4.65	2.61	
Respiratory acidosis (11) versus normal (29)	12.36	3.11	<0.001
	4.65	2.61	
Respiratory alkalosis (30) versus normal (29)	5.37	2.54	0.293
	4.65	2.61	
Mixed acidosis versus normal (29)	9.33	2.08	0.005
	4.65	2.61	
Respiratory acidosis (11) versus respiratory alkalosis (30)	12.36	3.11	<0.001
	5.37	2.54	
Respiratory acidosis (11) versus metabolic alkalosis (3)	12.36	3.11	0.001
	4.67	0.58	
Metabolic acidosis (24) versus respiratory alkalosis (30)	12.92	3.92	<0.001
	5.37	2.54	
Respiratory alkalosis (30) versus metabolic alkalosis (3)	5.37	2.54	0.642
	4.67	0.58	

ABG: Arterial blood gas, ICU: Intensive care unit

stay value of 5.2. Thus, alkalosis does not play a role in increasing the ICU stay.

The mean ICU stay of metabolic acidosis and metabolic alkalosis shown a statistically significant difference and it confirms that patients presented with metabolic acidosis had increased ICU stay.

The mean ICU stay of metabolic acidosis and respiratory acidosis showed statistically insignificant. Thus, patients who presented with respiratory and metabolic acidosis did not show the difference in their ICU stay.

The mean ICU stay of metabolic acidosis and respiratory alkalosis was shown a statistically significant difference and confirm that patients who presented with metabolic acidosis had increased ICU stay.

The mean ICU stay of metabolic acidosis and mixed acidosis showed statistically insignificant. Thus, it is proved that patients presenting with metabolic acidosis and mixed acidosis did not show variation in their ICU stay.

The ICU stay of patients presenting with respiratory acidosis and respiratory alkalosis was shown a statistically significant difference and it was confirmed that patients presenting with respiratory acidosis had increased ICU stay.

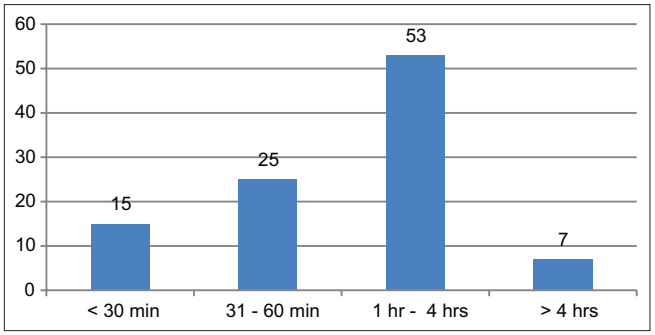

Figure 3: Presentation at hospital after consumption

The ICU stay of patients presenting with metabolic alkalosis and respiratory alkalosis was shown a statistically insignificant. Thus, it is proved that patients presenting with metabolic and respiratory alkalosis did not show the difference in their mean ICU stay.

The mean ICU stay of patients presenting with respiratory acidosis and metabolic alkalosis was shown a statistically significant difference and it confirms that patients presenting with respiratory acidosis had increased ICU stay [Figure 4 and Table 1].

DISCUSSION

The diagnosis of OP pesticide poisoning is based on the patient's history, clinical presentation, and laboratory tests. In a patient with a positive history, a typical odor

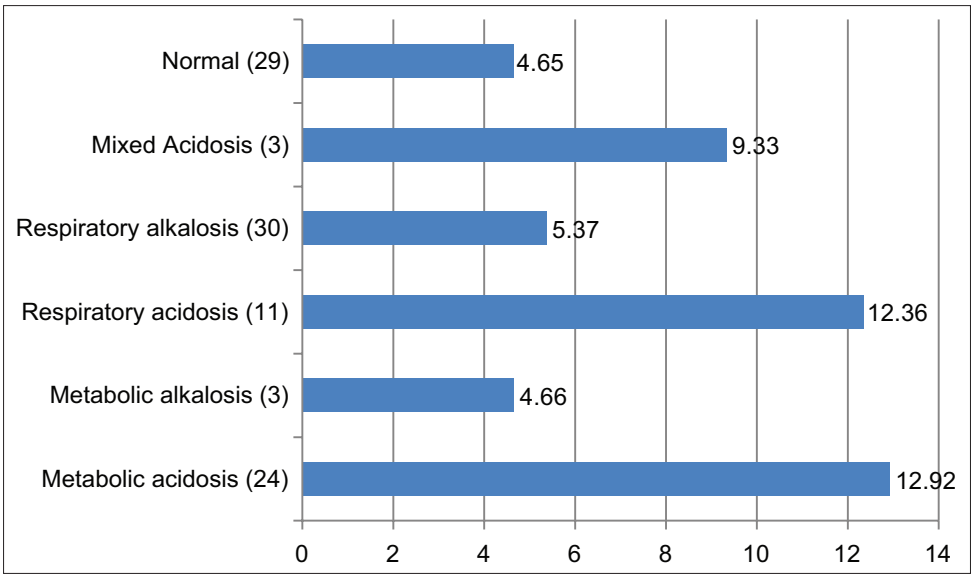

Figure 4: Mean days of intensive care unit stay versus arterial blood gas analysis interpretation

on the breath, characteristic symptoms, and depressed erythrocyte and plasma cholinesterase activities, diagnosis is not difficult to make. Unfortunately, history is often unobtainable. Moreover, the clinical features of OP poisoning may not be recognized as such if the patient presents, for example, with heart block, gastroenteritis, convulsions, or ketoacidosis. An awareness of this diversity of presentation is the first step to an accurate diagnosis.

In OP poisoning, OPC inhibits acetylcholinesterase activity, increases the accumulation of acetylcholine in the synaptic gap, and decreases degradation of acetylcholine, thus leading to excessively increased cholinergic symptoms, which disturbs neurotransmission of the central and peripheral nervous system. This excess synaptic acetylcholine stimulates muscarinic receptors and then depresses or paralyzes the nicotinic receptors. Abnormal neuromuscular transmission mediated through nicotinic receptors may cause carbon dioxide retention and alter the acid-base balance.[8] A retrospective analysis of OP poisoning patients, carried by Liu *et al.*, found a direct correlation between the severity of poisoning and mortality and the presence of pre-treatment of metabolic and respiratory acidosis.[11]

Among the patients who presented with acidosis, extreme acidosis (<7.1) was associated with increased ICU stay when compared with mild-to-moderate acidosis. Patients who presented with alkalosis had decreased ICU stay irrespective of their ranges. Death was reported in 6% of cases. Among them, 3% were cases who presented with metabolic acidosis; 2% with respiratory acidosis; and 1% with mixed acidosis. Thus, the present study showed that among the acid-base disorders in the initial ABG in OP poisoning patients, acidosis was associated with increased morbidity. In patients presenting with acidosis, metabolic acidosis is predominantly associated with increased morbidity and mortality followed by respiratory acidosis subsequently. Mixed acidosis ranks the third in increasing the morbidity and mortality of the patients presenting with OPC poisoning. Metabolic alkalosis and respiratory alkalosis were associated with decreased morbidity and no death was reported in these cases.

Metabolic acidosis is one of the frequent complications of OP poisoning and has been documented as an important determinant of the outcome of the patient.[11] However, severe metabolic acidosis, refractory to standard treatment measures such as sodium bicarbonate, is a rarely reported complication and invariably indicates a poor prognosis. Examples can be cited in four cases with severe metabolic acidosis and hypotension that did not respond to catecholamines.[12]

Most of the patients presented to the ED within 1–4 h of ingestion. Most of them had received gastric lavage in the pre-hospital care setup. In all the cases, ABG, serum cholinesterase levels, electrolytes, and other routine biochemical investigations were carried out. Serum cholinesterase was mostly lowered in all cases suggestive of OP poisoning. Arterial blood was drawn for acid-base analysis. Around 71% of cases had acid-base disturbances, whereas only 29% had normal ABG reports. According to Moulali *et al.*, the study which involved 20 cases 85% had acid-base disturbance and 15% had normal ABG reports.[13]

CONCLUSION

The present study highlights the importance of ABG as an effective tool in the quick assessment of prognosis in

OP poisoning patients. From this study, it is evident that the initial ABG performed on patients presenting with OP poisoning could help in determining the prognosis of the patients even before hospitalization. Special consideration should be given to patients presenting with acidosis (metabolic, respiratory, and mixed) as it is concluded from this study that acidosis (predominantly metabolic acidosis) is associated with increased morbidity and mortality. As a result, the treatment can be intensified and implemented quickly without any delay.

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Original Article

The Spectrum of Clinical Presentations of Gestational Trophoblastic Disease from a Tertiary Care Center

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Abstract

Introduction: Gestational trophoblastic disease (GTD) is a disease of pregnancy and therefore a disease of women. GTD comprises the heterogeneous group of related lesions arising from abnormal proliferation of trophoblast of the placenta with a spectrum of disorders ranging from benign to malignant disease. The malignant form of GTD collectively called gestational trophoblastic neoplasia (GTN).

Aim: The aim of this study was to analyze the clinical characteristics, outcomes, and factors affecting response to treatment.

Materials and Methods: We undertook a retrospective review of GTD cases treated at our center from 2017 to 2019, in which patients demographic profile and clinical information were identified including age, gravidity, symptoms, gestational age, consanguinity, pathologic diagnosis, investigations, treatment, and follow-up data, and subsequently, statistical analysis was done.

Results: During the 3-year period, 78 cases of GTD were reviewed. Complete and partial molar pregnancies were diagnosed in 49 (68%) and 29 (32%) cases, respectively. According to the International Federation of Gynecology and Obstetrics anatomical staging, the most GTN patients were assessed as Stage I and Stage III, at 80.0% and 11.4%, respectively. Post-molar GTN developed more frequently in women who had a pathologic diagnosis of complete mole, uterus larger than 14-week size, and pretreatment human chorionic gonadotropin levels more than 150,000 mIU/mL. Our study demonstrated a superior response to single-agent actinomycin D (90%). The overall cure rate at our center approached 96% during the study period.

Conclusion: GTD results in significant maternal morbidity, which leads to mortality if not detected early. The patients should be risk stratified for proper management and referred to experienced centers that have capabilities for adequate supportive care and consequent treatment.

Key words: Beta-human chorionic gonadotropin, Gestational trophoblastic disease, Gestational trophoblastic neoplasia, Hydatidiform mole

INTRODUCTION

Gestational trophoblastic disease (GTD) is a disease of pregnancy and therefore a disease of women. GTD comprises a heterogeneous group of related lesions arising from abnormal proliferation of trophoblast of the placenta with a spectrum of disorders ranging from benign to malignant disease.[1] The malignant form of GTD collectively called gestational trophoblastic neoplasia (GTN). It includes benign non-neoplastic lesions, hydatidiform mole (HM), and GTN. GTD is more common in extremes of reproductive age; women in early age or perimenopausal are at higher risk.

Asian ethnicity[2] is an important risk factor for GTD, and risk assessment can be estimated by a modified World Health Organization (WHO) scoring system and International Federation of Gynecology and Obstetrics (FIGO) staging system. Overall, GTD carries a good prognosis.[3]

The incidence of HM is difficult to establish with certainty due to the low frequency of the disease and regional

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variation in reported rates. The hormone beta-human chorionic gonadotropin (HCG) is essential for diagnosis, the management, or subsequent surveillance of GTD. The introduction of routine ultrasonography in early pregnancy is diagnostically reliable to confirm GTD and follow-up with them. Since GTD is a histologic diagnosis, it is essential to have an accurate histopathology examination and subsequently with adequate treatment based on staging.

Aim

The aim of this study was to analyze the clinical characteristics, outcomes, and factors affecting response to treatment.

MATERIALS AND METHODS

The medical records of all GTD patients who were diagnosed at the Institute of Obstetrics and Gynaecology, Egmore, Chennai, from January 2017 to December 2019 were retrospectively analyzed. For patients with a molar pregnancy, demographic profile and clinical information were identified including age, gravidity, symptoms, gestational age, consanguinity, pathologic diagnosis, investigations, treatment, and follow-up data. The biochemical profile includes complete blood counts, renal function, liver function tests, and serum beta-HCG estimation which were done. Measurement of serum beta-HCG levels was performed by chemiluminescent enzyme immunoassay. The normal level of serum beta-HCG was defined as lower than 5 mIU/Ml. Suction curettage was the recommended method of molar pregnancy treatment for most patients who were then monitored with weekly serum HCG measurements until the levels were normal for 3 consecutive weeks and then with monthly measurements for at least 12 months. Contraception was recommended, preferably with combined oral contraceptive pills. Post-molar GTN was diagnosed using the following criteria:[4]

1. Rise of serum HCG levels of 10% or greater for three values over 2 consecutive weeks
2. Plateau of serum HCG levels (rise or decline of <10%) for four values over 3 consecutive weeks
3. Histological diagnosis of choriocarcinoma
4. Presence of metastatic disease and
5. Persistence of serum HCG level in the 6 months after termination of pregnancy.

In the case of GTN patients, clinical information including age, parity, antecedent pregnancy, symptoms, pre-treatment serum HCG levels, treatment, and follow-up data were identified. The extent of disease was evaluated by chest radiography, ultrasonography, and/or magnetic resonance imaging. Planning the management of GTD patients was assigned based on the FIGO anatomic staging system and the modified WHO prognostic scoring system.[5] All GTN patients were categorized as follows:

1. Low-risk disease if Stage I or Stages II–III, score <7 and
2. High-risk disease if Stages II–III, score equal or more than 7, or Stage IV.

Single-agent chemotherapy (methotrexate or actinomycin D) was the treatment of choice for patients with low-risk disease, whereas combination chemotherapy was considered in patients with high-risk disease. The preferred combination regimen consisted of etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine. During treatment, patients were monitored with weekly serum HCG measurements until normal, after which additional consolidation therapy was utilized (low risk: 1 cycle and high risk: 3 cycles). Patients were considered to be in remission when 3 consecutive weekly serum HCG measurements were at normal levels. The resistant disease was indicated when the following occurred:[6]

1. Rising of serum HCG levels over a cycle
2. Plateau of serum HCG levels for 2 consecutive cycles or
3. Presence of new metastasis.

After HCG remission was achieved, the patients were scheduled for monthly serum HCG measurements and ultrasonography abdomen for at least 12 months in Stages I–IV. Contraception was also recommended preferably with combined oral contraceptive pills. The relapsed disease was diagnosed when the serum HCG levels rose after achieving an initial remission. Patients with the resistant or relapsed disease received second-line chemotherapy. Statistical analysis of the data was carried out and demographic data were determined using percentage, mean, and standard deviation (SD). Comparisons between groups were performed using the Student's *t*-test and Chi-square test. $P < 0.05$ was considered statistically significant.

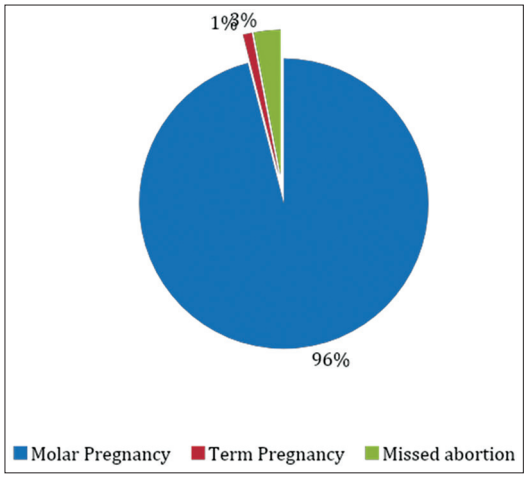

Figure 1: Antecedent pregnancy

RESULTS

During the 3-year period, 78 cases of GTD were reviewed, of which 45 HM and 33 cases of GTN were identified. Two patients of HM and two GTN patients were lost to follow-up. The mean age at diagnosis was 24.03 ± 6.6 years. The median gestation age was 11.04 weeks (range 3.20) and 59 cases (75%) were diagnosed in the first trimester. Seven patients had a history of previous molar pregnancy.

Pre-treatment serum HCG levels were assessed in 78 cases, with a mean level of 96,317. In our study only 2 cases had clinical hyperthyroidism. All molar pregnancies were terminated by suction curettage. Abnormal uterine bleeding was the most common presenting symptom (57.4%) [Table 1], while 33% of patients were asymptomatic. Theca lutein cysts were found in 3.8% of patients and only one patient developed GTD following term pregnancy.

Complete and partial molar pregnancies were diagnosed in 49 (63%) and 29 (37%) cases, respectively, whereas 45 molar pregnancy patients (59%) had the spontaneous achievement of remission [Tables 2 and 3 and Figure 1].

Among 78 GTD patients', molar pregnancy observed in 75 patients (96.10%) while terming pregnancy and missed abortion result in 1.30% and 2.60% of cases, respectively.

Among GTD patients, 49 (62%) were complete mole while partial mole in 29 (32%) cases. GTD developed following term pregnancy in 1 (1.3%) case while missed abortion observed in 2 (2.6%) patients. Consanguinity observed in 9 (11.5%) patients.

Most GTN patients (63.6%) had a serum HCG titer of <100,000 mIU/ml. According to the FIGO anatomical staging, most GTN patients were assessed as Stage I and Stage III, at 80.0% and 11.4%, respectively. Among seven metastatic patients, lung involved in four cases while vulvovaginal and brain metastasis observed in two and one cases, respectively. The GTN patients were divided into a low-risk and a high-risk group, comprising 77% and 23% of cases, respectively.

To determine the possible risk factors for developing post-molar GTN, comparisons were made between these two groups of patients. Post-molar GTN developed more frequently in women who had a pathologic diagnosis of complete mole, uterus larger than 14-week size, and pre-treatment HCG levels more than 150,000 mIU/mL. Table 3 displays the clinical characteristics of GTN pregnancy patients. The mean age at diagnosis was 25.24 years (SD, 5.8) Table 4. The median time interval from pregnancy events to treatment was 3 months.

Table 1: Study parameters of patients

Parameters	Number of patients	Percentage
Age in years		
<20	19	24.3
20–25	38	48.7
25–30	15	19.2
More than 30	6	7.6
Gravida		
Primi	37	47
Multi	41	53
Presenting complaints		
Abdominal pain	4	5
Asymptomatic	25	33
Bleeding	45	57
Hyperemesis	4	5

Table 2: Distribution of diagnosis and outcome

Parameters	Number of patients	Percentage
Diagnosis		
Complete	49	63
Partial	29	37
Outcome		
Invasive mole – Req. chemo	33	41
Non-invasive mole	45	59

Table 3: Symptoms (invasive mole)

Presenting complaints	Number of patients, *n* (33)
Bleeding	21
Asymptomatic	9
Abdominal pain	1
Hyperemesis	2

Table 4: Demographic characteristics (invasive mole)

Age in years (mean±SD)	25.24±5.89
GA at diagnosis in weeks (mean±SD)	12.33±1.85
Pre-treatment beta-HCG (mean±SD)	136,664±74,228

HCG: Human chorionic gonadotropin, SD: Standard deviation, GA: Gestational age

Table 5: Pre-treatment beta-HCG

Outcome	Mean	SD	*P*-value
Invasive mole	136,808	74,228	0.001
Non-invasive mole	96,317	9614	

HCG: Human chorionic gonadotropin, SD: Standard deviation

Table 6: Type of GTD versus histopathology

Type of GTD	Invasive	Non-invasive	*P*-value
Complete mole	26	21	0.007
Partial mole	7	22	

GTD: Gestational trophoblastic disease

Table 7: WHO score

WHO score	GA at diagnosis		*P*-value
	Mean	SD	
<7	10.67	3.2	0.012
More than or equal to 7	14.57	3.5	

GA: Gestational age, WHO: World Health Organization, SD: Standard deviation

Table 8: Disease category/chemotherapy

Chemotherapy	Number of patients (*n*)	Complete remission (%)
Single-agent methotrexate	18	13 (74)
Single-agent actinomycin D	7	6 (90)

Pre-treatment beta-HCG versus outcome [Table 5], type of GTD versus histopathology [Table 6], and WHO score versus gestational age at diagnosis [Table 7] showed a statistically significant correlation in our study.

All GTN patients received chemotherapy, the overall complete remission rate to the initial regimen was 79%; we observed a complete remission rate of 74% in patients treated with single-agent methotrexate, while the remission rate was 90% in patients treated with single-agent actinomycin D [Table 8]. Higher WHO score (5–6) associated with increased resistance to single-agent chemotherapy. Eventually, the cure rate of the low-risk patients approached 100% excluding lost follow-up cases, but two cases in the high-risk group are in salvage chemotherapy.

DISCUSSION

The incidence[7] of GTD varies widely in different regions and ethnicities of the world. The incidence of HM appears to be about 0.5–1/1000 deliveries in most parts of the world. The majority of women diagnosed with GTN can be cured with an overall worldwide survival rate of the low-risk group approaching 100% and 80–90% for high-risk group.[8-13] However, these tumors are rare in any individual hospital and most treatment recommendations are based on observational studies from larger series. Our Institute of Obstetrics and Gynaecology, Egmore, Chennai, has become a referral center and many patients were directed to our center from all across Northern Tamil Nadu. In this series of 78 patients spanning over 3 years of period, we confirm the previously reported highly curable rates of GTN when therapeutic decisions are based on the FIGO anatomic stage and the WHO prognostic scoring index. The overall survival rate for patients with GTN treated at our center approached 96%.

In the present study, a history of the previous molar pregnancy, extremes of maternal age, and consanguinity were found to have risk factors associated with molar pregnancy. This is in accordance with the previous studies. In our study, especially younger maternal age is more commonly observed as a risk factor.

The median gestational age at diagnosis of molar pregnancy of 12[8,14,15] weeks found in the present study was consistent with other studies in centers with routine first-trimester ultrasound. In the present study, abnormal uterine bleeding was the most common presenting symptom[8,15] (60%) of molar pregnancy; on the other hand, the identification of asymptomatic patients was 25%, which was also in accordance with the previous studies (29–41%). The frequency of theca lutein cysts (3.8%)[16,17] in this study was lower than that found in other studies, in which the rates were 20–46%.

Post-molar GTN developed more frequently in women who had a pathologic diagnosis of complete mole, uterus larger than 14-week size,[18] and pre-treatment HCG levels more than 150,000 mIU/mL. Higher WHO score (5–6) even it is considered as the low-risk associated with increased resistance to single-agent chemotherapy.

Patients with low-risk GTN can usually be treated successfully with single-agent chemotherapy. In our series of 27 low-risk patients, we observed a complete remission rate of 74% to single-agent methotrexate and 90% to single-agent actinomycin D.[19] In keeping with our results, other peer-reviewed studies have also reported the superiority of single-agent actinomycin D over methotrexate as frontline therapy in low-risk patients. A randomized clinical trial comparing biweekly actinomycin D to weekly IM methotrexate has demonstrated a superior response rate for actinomycin D over methotrexate.

CONCLUSION

Clinical characteristics and outcome are comparable with other studies happened in developing countries. Histological diagnosis of complete mole, higher gestational age, and pre-evacuation beta-HCG of higher than 150,000 mIU/mL was significant factors for developing post-molar GTN. The patients should be risk stratified for proper management and referred to experienced centers that have capabilities for adequate supportive care and consequent treatment.

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Original Article

Comparison of Imagiology with Operative Findings in a Case of Intestinal Obstruction

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Abstract

Introduction: The diagnosis of intestinal obstruction is a team work of radiologist and clinician. Acute abdominal conditions require precise radiological diagnosis to achieve excellent results to reduce morbidity and mortality.

Aims and Objectives: This study aims to study the various radiographical, ultrasonographic, and contrast-enhanced computerized tomography (CECT) findings associated with intestinal obstruction and to study the various causes of intestinal obstruction.

Methodology: A prospective study of 50 patients admitted to the Mahatma Gandhi Memorial (MGM) Hospital, Warangal, during the period of November 2017–September 2019 with the diagnosis of intestinal obstruction.

Results: A clinical study of 50 cases of intestinal obstruction was done at Osmania hospital at Hyderabad during November 2017–September 2019. Intestinal obstruction whether in small bowel or large bowel occurs nearly in equal ratio in both sexes.

Conclusion: Intestinal obstruction remains still a common and important surgical emergency. Obstruction due to adhesions increasing in incidence due to increased abdominal and pelvic surgeries. X-ray erect abdomen and ultrasonography abdomen are able to diagnose intestinal obstruction, but CECT has more sensitivity and specificity in diagnosing the intestinal obstruction. It also helps in the management of the intestinal obstruction.

Key words: Adhesions, Bands, Computerized tomography scan, Hernia, Intussusception, Large intestine, Malignancy, Resection and anastomosis, Small intestine, Stricture, Tuberculosis of intestine gangrenous bowel, Ultrasonography, Volvulus

INTRODUCTION

Intestinal obstruction is a common surgical emergency all over the world. It is defined as obstruction in forward propulsion of the contents of the intestine either due to dynamic, adynamic, or pseudo-obstruction. It is predisposed by varying underlying anomalies and diseases which are difficult to define preoperatively. Although intestinal obstruction can be diagnosed easily, the underlying cause except post-operative adhesions and external hernias is difficult to be diagnosed preoperatively. Early diagnosis of obstruction, pre-operative preparation, skillful operative management, proper technique during surgery, and intensive post-operative treatment carries a grateful result. The diagnosis and management of the patient with intestinal obstruction is one of the more challenging emergencies that a general surgeon can come across. Although the mortality due to acute intestinal obstruction is decreasing with better understanding of pathophysiology, improvement in diagnostic techniques, fluid and electrolyte correction, much potent antimicrobials, and surgical management, still mortality ranges from 3% for simple obstruction to as much as 30% when there is a vascular compromise or perforation of the obstructed bowel.

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Aims and Objectives

The aims of the study were as follows:

1. To study the various causes of intestinal obstruction.
2. To study the various radiographical, ultrasonographic, and contrast-enhanced computerized tomography (CECT) findings associated with intestinal obstruction.

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3. To analyze the efficacy of CECT in predicting the etiology of intestinal obstruction and its correlation with intraoperative findings.

METHODOLOGY

A prospective study of 50 patients admitted to the Mahatma Gandhi Memorial (MGM) Hospital, Warangal, during the period of November 2017–September 2019 with the diagnosis of intestinal obstruction. Investigations and operative findings were collected from inpatients where interpreted 50 patients who presented to us with intestinal obstruction were admitted to the hospital in the above-mentioned period and were subjected to plain X-ray of abdomen, ultrasonography (USG), and CECT of abdomen.

All patients included in the study were examined thoroughly and history, physical examination, and investigation findings were recorded as per pro forma. After a history taking and physical examination, all patients underwent plain X-ray abdomen, USG, and CECT abdomen. Plain X-ray abdomen anteroposterior view with horizontal beam in upright position was taken. This film included both domes of diaphragm and pelvis up to the symphysis pubis. Confirmation of the imagiology was done by intraoperative findings. Finally, effort was made to study the sensitivity of plain X-ray, ultrasonographic, and CECT abdomen findings to final diagnosis: Efficacies were analyzed.

RESULTS

A clinical study of 50 cases of intestinal obstruction was done at Osmania hospital at Hyderabad during November 2017–September 2019, Warangal, studied as follows [Tables 1-12]:

Table 1: The age and sex distribution of the cases

Age group	Male	Female	Total	Percentage
11–20	2	4	6	12
21–30	5	2	7	14
31–40	5	4	9	18
41–50	6	4	10	20
51–60	4	6	10	20
61–70	5	3	8	16
Total	27	23	50	100

Table 2: Presenting symptoms and signs

S. No.	Clinical features	Number of cases	Percentage
1.	Pain abdomen	50	100
2.	Vomiting	43	86
3.	Distension of abdomen	50	100
4.	Constipation	30	60
5.	Dehydration	30	60
6.	Fever	7	14
7.	Tenderness over the abdomen	40	80
8.	Guarding	20	40
9.	Palpable mass	13	26
10.	Increased bowel sounds	44	88
11.	Absent bowel sounds	6	12

CECT: Contrast-enhanced computerized tomography

Table 3: Sensitivity and specificity of CECT in diagnosing adhesions in intestinal obstruction

Statistic	CECT in intestinal obstruction (%)
Sensitivity	95
Specificity	96.67
Positive predictive value	95
Negative predictive value	96.67

CECT: Contrast-enhanced computerized tomography

Table 4: Sensitivity and specificity of CECT in diagnosing hernia in intestinal obstruction

Statistic	CECT in intestinal obstruction (%)
Sensitivity	87.5
Specificity	95.2
Positive predictive value	77.78
Negative predictive value	97.50

CECT: Contrast-enhanced computerized tomography

DISCUSSION

Intestinal obstruction continues to be a frequent emergency, which surgeons have to face 1–4% of emergency operations. Richard *et al.* analyzed 1000 consecutive abdominal surgeries in 1976 and reported an incidence of 2.5%.[1] In 1973, reported an incidence of 3.2%.[2] In our hospital, 1574 cases of total abdominal surgeries were done in November 2017–September 2019, of which 50 cases were intestinal obstruction comprising about 3%. The involvement of small bowel in obstruction is much more common than that of large bowel.[3] The delay in the treatment will lead to high mortality. Since the advancement in understanding the anatomy/physiology, fluid and electrolyte management along with modern antibiotics, and intensive care unit, the mortality has been decreasing consistently.[4] The associated medical problems (such as respiratory cardiac or metabolic diseases) and advanced age carry a considerable contribution in adding the mortality.

Age Incidence

Although intestinal obstruction occurs in all age groups, here the youngest patient was 14 years and oldest patient was 70 years. In this study, 20% belongs to 50–60 years age group and 58% belongs to 30–60 years age group. Studies by Gill and Eggleston[5] have reported 17% of cases in the

age group of 50–60 years and 60% of the cases of intestinal obstruction occur in the age group of 30–60 years. Their studies almost correlate with the present study. However, studies reported by Singh *et al.*[6] and Ramachandran[7] say that the maximum number of cases occur in the age group of 21–40 years, of these the etiological factors were obstructed hernia. The explanation which I would like to give in presently the etiological shift is toward adhesions and then hernia, which are decreasing from the earlier 20th century most common cause of intestinal obstruction due to awareness as people are seeking treatment early for hernia.

Table 5: Sensitivity and specificity of CECT in diagnosing TB stricture in intestinal obstruction

Statistic	CECT in intestinal obstruction (%)
Sensitivity	80
Specificity	95.56
Positive predictive value	66.67
Negative predictive value	97.73

CECT: Contrast-enhanced computerized tomography, TB: Tuberculosis

Table 6: Sensitivity and specificity of CECT in diagnosing volvulus in intestinal obstruction

Statistic	CECT in intestinal obstruction (%)
Sensitivity	66.7
Specificity	97.8
Positive predictive value	66.7
Negative predictive value	97.8

CECT: Contrast-enhanced computerized tomography

Table 7: Sensitivity and specificity of CECT in diagnosing malignancy/mass in intestinal obstruction

Statistic	CECT in intestinal obstruction (%)
Sensitivity	85.7
Specificity	97.7
Positive predictive value	85.8
Negative predictive value	97.7

CECT: Contrast-enhanced computerized tomography

Table 8: Age-wise incidence of intestinal obstruction in different studies

Age group	Singh *et al.*	Playforth	Cole	Gill	Present study (%)
11–20	10%	4	10	12	12
21–30	16	5	10	12	14
31–40	18	13	18	13	18
41–50	15	18	16	13	20
51–60	10	14	15	16	20
>60	20	40	16	13	16

Sex Incidence

In the present study, there are 27 males and 23 females. Males and females are nearly in equal ratio. Among the previous studies, Budharaja *et al.*[9] and Singh *et al.*[6] reported 4:1 and Sufian and Matsumoto[3] found equal incidence.

Etiology

The etiology of intestinal obstruction varies from one country to other and from one part of the country to another party. The comparative study of the previous report is as follows:

The most common etiological factor in the present study is adhesion which included post-operative, inflammatory, and congenital bands. Post-operative adhesion occurs in 93% of cases of previous abdominal surgery, of every third patient will be having one of the other clinical signs and symptoms related to adhesion. Among 93% of the post-operative adhesions, 5% of the cases can develop acute intestinal obstructions, most of them will be within the 1st year (39–60%).

In the present series, 42% of the cases of obstruction are due to adhesion and bands. Among adhesion and bands, 61.9% are due to post-operative adhesion, 23.8% are due to inflammatory adhesions, and 15.3% are due to congenital bands.

McIver found that 80% of adhesions and 21% are due to congenital causes, Perry *et al.* found that 79% were post-operative adhesions, 18% inflammatory, and 28% were congenital. In the inflammatory causes, 42% followed acute appendicitis, 14.5% diverticulitis, and others resulted from pelvic infection, Crohn's disease, and cholecystitis.

Table 9: Comparison of causes of intestinal obstruction in different studies

Cause	Present study (%)	Gill and Eggleston (%)[5]	Cole (%)	Playforth (%)	Ramachandran (%)[7]	Brooks and Buttler (%)	Biarj *et al.* (%)[8]
Adhesion	42	15	15	10	23	23	53
Hernia	20	27	27	35	13.6	25	26
Intussusception	-	12	12	12	7.4	18	-
TB	14	3.5	3.5	3	8.6	-	-
Malignancy	16	3.4	3.4	4	9.3	5	-
Volvulus	8	3.4	25	4	26.6	1	3
Mesenteric vascular thrombosis	-						26

TB: Tuberculosis

Table 10: Comparison of hernia causing intestinal obstruction in different

S. No.	Studies	Percentage
1.	Gill and Eggleston[5]	15
2.	Cole	15
3.	Playforth	10
4.	Ramachandran[7]	23
5.	Brooks and Buttler	23
6.	Biarj *et al*.[8]	53
7.	Present study	20

Table 11: Comparison of intestinal TB causing intestinal obstruction in different studies

TB in percentage		
Harbans *et al*.[6]	1972	17.2
Ramachandran[7]	1982	8.6
Present study	2017–19	14

TB: Tuberculosis

Table 12: Comparison of malignancy causing intestinal obstruction in different studies

Studies	Number of cases	Malignancy (%)
Harbans *et al*.[6]	53	15
Kostner *et al*.	300	53
Present study	50	16

On review of the earlier Indian studies, 10% of intestinal obstructions were related to adhesion and more recent studies in 1982 report 23%. The rise in the incidence of adhesions related obstructions is attributed to increased number of abdominopelvic surgeries. In the Western studies, the adhesion-related obstruction ranges from 40% to 60%. Developing countries like Virginia also reported 40% of the obstructions related to adhesions.

Hernia

In the present series, 10 cases of obstruction are related to hernia (20%) of cases. Among the obstructed hernias, 7 cases are due to obstructed inguinal hernia and the remaining 3 cases are due to obstructed incisional hernia. The comparative analysis of incidence of various studies reported the incidence from 13% to 35%. However, hernia-related obstructions were higher in the early 20th century, but due to early surgical treatment for hernia, the incidence is decreasing.

Tuberculosis

Tuberculosis is one of the common health problems in developing countries. In the present series, tuberculosis found to be a causative factor in 7 cases (14%) in the form of iliocecal tuberculosis with stricture and adhesions.

Our present study corresponds well with the other Indian studies by Harbans *et al*. However, disparity with Western literature is due to the increase in number of tuberculosis patients in the rural population.

Malignancy

Harbans *et al*. reported an incidence of 15% of bowel obstruction. In the present study, 8 cases (16%) presented with acute intestinal obstruction, five cases due to large bowel malignancy and three due to small intestinal malignancy. In large bowel malignancy, two at the descending colon, 2 at the transverse colon, in that 1 due to carcinoma of the stomach infiltrating transverse colon. In small intestine malignancy, 1 at the jejunum and 1 at the ileum due to carcinoid tumor, and the other 1 case is due to ovarian malignancy with intraperitoneal metastasis causing ileal obstruction.

The incidence of large bowel obstruction is higher in Western countries due to various factors, which includes increased aged population, consumption of high animal fat, and lack of fiber diet.

This present study correlates with Harbans *et al*. mentioned above.

Carcinoid Tumors Causing Small Intestine Obstruction

In our study, we found two interesting cause of intestinal obstructions, i.e., carcinoid tumors in jejunum and ileum, one case each.

Lubarsch first described carcinoid tumors in 1888. Oberndorfer used the term "karzinoide" to describe it in 1907. Carcinoid neoplasms are neuroendocrine tumors from enterochromaffin cells present as benign to malignant.

Carcinoid tumors involving the small intestine should, however, be regarded as malignant. They are most commonly found in the ileum, 73% of malignant carcinoids are found at this site, 4% in the jejunum. Small bowel carcinoid tumors usually present with intestinal obstruction, in 40% of cases, metastasis is found at laparotomy. About 4% of patients with small bowel carcinoid tumors develop carcinoid syndrome characterized by flushing, intestinal hypermotility, and bronchospasm.

Volvulus

Sigmoid volvulus is the common cause of large bowel obstruction. In our study, we had two cases of sigmoid volvulus and two cases of small bowel volvulus. Total percentage of volvulus in our study is 8%. Small bowel volvulus is a rare but life-threatening surgical emergency. The etiology may be primary where cause is not known and secondary due to adhesions and bands; Iwuagwu *et al*.,

1999, reported an incidence of 3.5–6.2%. Our study had 4% of small bowel volvulus. This corresponds to the study done by Iwuagwu *et al.*

Operations

All the cases of our study were subjected to surgery. The most common operation performed was resection of ileal segment and end-to-end ileoileal primary anastomosis 34%, release of adhesions and bands 30%. Hernia repair in 20%, hemicolectomy in 8% cases, reduction and untwisting of volvulus in 4%, resection of jejunal segment and end-to-end jejunoileal primary anastomosis 2%, and tube cecostomy in 2% of cases.

CONCLUSION

- Intestinal obstruction remains still an important surgical emergency
- Late presentation of the patient with complications possesses a challenging problem to the surgeons for management
- Patients with a clinical picture of obstruction of the bowel demand vigorous correction of fluid and electrolyte, which can be severe, and life threatening
- Post-operative adhesions are the common cause to produce intestinal obstruction as abdominal and pelvic surgeries are on rise
- X-rays are the first investigation to be done and USG abdomen and pelvis helps in differentiating between adyamic and dynamic obstruction. However, most of the due to gas shadow findings cannot be elicited correctly
- CECT helps in diagnosing the etiology better and gives good results for the management of intestinal obstruction
- Clinical, radiological, and operative findings put together can bring about the best and accurate diagnosis of intestinal obstruction
- Mechanical obstruction is not associated with any specific biochemical marker, which can help the surgeon for differentiate simple obstructions from ischemia or a closed-loop obstruction with impending bowel infarction. Diagnosis of strangulation is still a challenge
- Majority of the patients intestinal obstruction needs surgical relief of obstruction
- Early operation is mandatory to avoid the development of peritonitis and systemic sepsis associated with multisystem organ failure.

SUMMARY

A clinical study of 50 cases of intestinal obstruction was done at Osmania hospital at Hyderabad during November 2017–September 2019.

- Intestinal obstruction whether in small bowel or large bowel occurs nearly in equal ratio in both sexes
- Intestinal obstruction is more common in the age group of 30–60. Large bowel obstruction is more common in patients above 40 years than in younger group
- Small bowel obstruction is more common than large bowel obstruction
- Pain abdomen, vomiting, distension, and constipation are the four cardinal features of intestinal obstruction, present in most of the cases
- Plain X-ray abdomen taken in erect posture is the first most important investigation required for the patients
- Most common etiological factor for intestinal obstruction is adhesions due to post-operative and inflammatory causes.

The advancement in imagiology lead, especially CT scan and with contrast led to increase in accuracy in diagnosing the etiology of intestinal obstruction, has improved a lot; hernia is the second most common cause of intestinal obstruction. Intestinal tuberculosis with stricture is next common cause of intestinal obstruction.

- Malignant obstruction is far more common in large bowel than in small bowel. In large bowel, malignant obstruction is more common on the left side than the right side
- Volvulus is next common cause of intestinal obstruction. Sigmoid volvulus is the most common in large bowel obstruction
- Intravenous fluids and electrolytes, gastrointestinal aspiration, antibiotics, and then appropriate surgery are still the mainstay of the treatment.

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