ORIGINAL ARTICLE

CHRONIC KIDNEY DISEASE AND RISK FACTOR PREVALENCE IN DEHRADUN DISTRICT

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ABSTRACT

Objectives: The study was conducted to assess the prevalence of risk factors for Chronic Kidney Disease and to find out the prevalence of CKD.

Methodology: A community based survey was conducted in the selected urban wards of the district Dehradun to collect the required information of the study. Individuals aged between 40 – 80 years, residents of the area for at least one year were included in the study. Information regarding number of households and population in each ward was obtained. They were informed about the purpose of study. The household in each ward was selected on PPS basis. Out of each selected household, study subject (40-80yrs) was drawn on the basis of "Kish" method basis. After obtaining the written informed consent, they were interviewed using the WHO (stepwise approach for NCDs) questionnaire and SCORED screening test tool to identify risk factors. The subjects who were at risk were screened for chronic kidney disease. The data was compiled, entered & analyzed using SPSS version 19.

Results: Raised BP, diabetes and cases of heart attack were more among males as compared to females. The prevalence of CKD was 2.1 percent. Proportion of CKD cases was almost same in both sexes. Chronic kidney disease prevalence was 1.1%, 5.1% and 8.2% in 50-59, 60-69 and >70 year age groups.

Conclusion: The prevalence of diseases like hypertension, diabetes was high in the urban population etc. The disease prevalence tends to increase with the advancing age.

Key words: Chronic Kidney Disease, risk factors, prevalence

INTRODUCTION

The economic development and changing lifestyle habits are posing a significant impact on the public health scenario. The increased prevalence of non communicable diseases and their risk factors are becoming a matter of worry. The climbing burden of lifestyle related disorders is likely to raise the burden on already limited resources of health sector. One such condition battling in India and other nations is increased prevalence of Chronic Kidney Disease (CKD) which is considered as a silent epidemic of 21st century.

The prevalence of CKD is estimated to be 8-16% worldwide.[1] The prevalence in Asia is not lower than that seen in Western countries. In the absence of a proper registry and paucity of population-based studies, exact prevalence of CKD in India is not known. Based on data from major tertiary care centers, the presumptive estimates of incidence of End Stage Renal Disease in India are 100 per million populations.[2] It is obvious that in a country like India, screening the whole population for CKD is neither required nor feassible. Thus, we need to concentrate on screening individuals at high-risk (e.g. people older than 50 years; people with a history of diabetes mellitus, hypertension, cardiovascular disease; or who have a family history of CKD) for CKD. The early detection of high-risk individuals is critical for both the development and implementation of strategies to prevent the progression to ESRD. Progress to kidney failure or other adverse outcomes could be prevented or delayed by early detection and treatment with population based screening.

Thus a community based study was conducted in the urban area of district Dehradun with the aim to determine, among at risk in general population, the prevalence of risk factors for Chronic Kidney Disease and the prevalence and association of risk factors in individuals with CKD

METHODOLOGY

The present study was conducted and sample size of 3300 was drawn from the prevalence of 12.3 % (According to study conducted in South India).[3] A community based survey was conducted in the se-

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SKIN ADVANCED GLYCATION END PRODUCTS (AGES), RAGE AND GLYOXALASE-I (GLO-I) ARE ASSOCIATED WITH DIABETIC NEUROPATHY IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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ABSTRACT

Introduction: Advanced Glycation End Products (AGEs), their receptor (RAGE) and their detoxifying enzyme Glyoxalase-I (GLO-I) have been implicated in the development of experimental diabetic peripheral neuropathy (DPN). However, few studies have assessed their role in the tissues of diabetic patients.

Aim: We have assessed the relationship between skin expression of AGEs, RAGE, GLO-I and diabetic neuropathy in patients with type 1 diabetes.

Materials and Methods: Sixty-two patients with type 1 diabetes mellitus (16 with and 46 without DPN) and 30 age-matched control subjects underwent detailed assessment of neurologic deficits, quantitative sensory testing, electrophysiology, corneal confocal microscopy (CCM) , intraepidermal nerve fibre density (IENFD) and AGEs, RAGE and GLO1-I expression in foot skin biopsies.

Results: Skin AGEs and RAGE expression was significantly higher and GLO-I was significantly lower in the epidermis, microvessels and reticular extracellular matrix ofpatients with diabetic neuropathy as compared to diabetic patients without neuropathy and control subjects.Skin AGEs and RAGE expression was also moderately but significantly increased and GLO-I expression was decreased in some skin structures in patients without diabetic neuropathy as compared to control subjects. Skin AGEs and RAGE expression correlated negatively and GLO-I expression correlated positively with sural nerve amplitude and velocity, IENFD and corneal nerve pathology.

Conclusion: These findings suggest that AGEs, RAGE and GLO-I may play an important role in the etiology of human diabetic neuropathy.

Keywords: Diabetic neuropathy, Advanced glycationendproducts (AGEs), RAGE, Glyoxalase-I

INTRODUCTION

Diabetic Peripheral Neuropathy (DPN) is one of the most common chronic complications of diabetes which affects around 50% of all diabetic patients and the main contributing factor for foot ulceration and amputation in diabetic patients.[1] Several mechanisms have been suggested linking hyperglycemia with DPN and include activation of the polyol pathway, oxidative/nitrosative stress, increased protein kinase C activity, enhancement of poly ADP-ribose polymerase, and particularly the increased expression of advanced glycation end products (AGEs) and their receptor (RAGE).[2]Several tests have been advocated to assess nerve damage in DPN including nerve conduction studies, quantitative sensory testing and nerve biopsy.[3] Recently, the less invasive skin biopsy have been used to assess intraepidemal nerve fibre (IENF) damage and Corneal Confocal Microscopy (CCM) have been used to assess corneal nerve fibres damage which correlated well with IENF findings.[3]

AGEs are heterogeneous molecules derived from non-enzymatic reaction between sugar moieties and amine residues of proteins, lipids and nucleic acids, as a consequence of sustained hyperglycemiaand their production is accelerated in diabetes mellitus (DM).[4,5] The main and best characterized receptor of AGEs is RAGE, a member of the immunoglobulin superfamily. AGE-RAGE binding triggers intracellular signalling, NF-kB activation and an inflammatory response accompanied by the release of cytokines, inflammatory cells and generation of reactive oxygen species.[6] The glyoxalase system is the physiological

dicarbonyl-detoxifying system where Glyoxalase-I (GLO-I), the rate-limiting enzyme, converts precursors of reactive AGEs into D-Lactate, thuspreventing AGEs formation.[7]

AGEs and RAGE have been linked to the chronic complications of diabetes including DPN, their progression [8] and recently to β-cells apoptosis.[9] There are also emerging data that connect the AGEs detoxifying enzyme, GLO-I with DPN [6] and its activity has been shown to be significantly lower in type 1 and type 2 DM patients with painful DPN.[10]Thus, alterations in AGEs, RAGE and GLO-I expression has been reported predominantly in animal tissues and there are only limited translational data in human plasma [5] and using human skin autofluorescence [11] to suggest they may play a significant role in the pathogenesis of DPN. However, plasma levels do not reflect tissue levels [12] and assessment of skin autofluorescence has limitations.[13]

We have had the unique opportunity to assess the expression of AGEs, RAGE and GLO-I in skin biopsies from the feet of diabetic patients with and without neuropathy. We have also explored the relationship of the expression of these proteins with the severity of neuropathy, which was quantified using a range of established and novel measures of human diabetic neuropathy.

METHODOLOGY

Ninety-two participants were enrolled in this study. Sixty-two patients with Type 1 diabetes mellitus and 30 healthy control subjects participated in this study. Neuropathy was defined according to the Toronto consensus [14]. DPN was defined as the presence of abnormal personal motor nerve conduction velocity (<42m/sec) and the presence of abnormal symptoms and signs of DPN (NDS score >2). Exclusion criteria includes non-diabetic causes of peripheral neuropathy, sever DPN (NDS>8),history of corneal traumatic injury or corneal surgery or systemic disease like cancer and congestive heart failure (grade III or VI). The study was approved by the Central Manchester Ethics Committee (Ref. no. 09/H1006/38) and written informed consent was obtained according to the declaration of Helsinki.

Assessment of Neuropathy: Symptoms were evaluated using the Neuropathy Symptom Profile [15]and painful symptoms were assessed by the short form McGill pain questionnaire [16]. Neurological deficits were assessed using the Neuropathy Disability Score (NDS), quantitative sensory testing (QST) involving the quantification of cold and warm thresholds using the Neuro Sensory Analyzer TSA-II (Medoc Ltd., Ramat Yishai 30095, Israel) [17]. Vibration perception threshold (VPT) was evaluated using a Neuroaesthesiometer (Horwell, Scientific Laboratory Supplies, Wilford, UK) [17]. Autonomic function (deep breathing heart rate variability DB-HRV) was assessed using a CASE IV automated system (WR Medical Electronics, Inc, Stillwater, MN, USA). Nerve conduction studies were performed by a consultant neurophysiologist using Medtronic Keypoint™ EMG system equipped with temperature regulator to maintain limb temperature in a range of 32-35°C. Peroneal motor and sural sensory nerves amplitudes and conduction velocities were assessed on the right foot.

All participants had both eyes scanned with a laser CCM (HRT III-RCM Heidelberg GmBH, Heidelberg, Germany) by purpose trained optometriststo obtain several scans of the entire corneausing previously published method[3]. Three parameters were quantified in each IVCCM image: Corneal Nerve Fibre Density (CNFD) - total number of major nerves/mm^2; Corneal Nerve Fibre Length (CNFL) - total length of all nerve fibres and branches (mm/mm^2) and Corneal Nerve Branch Density (CNBD) - number of branches emanating from major nerve trunks/mm^2.

Immunohistochemistry: Two 3 mm punch skin biopsies were taken from the dorsum of the feet, approximately 2 cm proximal to the second metatarsal head under local subcutaneous anesthesia (1% lidocaine). Immediately after collection, the biopsies were fixed in 4% buffered paraformaldehydefor 18-24 hours. One sample was used for IENFD assessment (frozen sections) using previously published method [18] while the second one was routinely processed to paraffin block for immunohistochemistry assessment. Intraepidermal nerve fibre density (IENFD) was calculated as the number of nerve fibres crossing the basement membrane of the epidermis per millimeter length of the epidermis.

The formalin-fixed paraffin-embedded tissue blocks were cut at 5μm thickness on a microtome (Leica Biosystems, Peterborough, UK). The deparaffinised and rehydrated sections were subjected to antigen retrieval in 0.1M citrate buffer pH 6.0.. Endogenous peroxidase was quenched with Dako Peroxidase-Blocking Solution (Dako Ltd, Denmark) and non-specific binding was blocked with 5% normal horse serum (NHS) for AGEs andGLO-I or normal goat serum (NGS) for RAGE. Consecutive sections were incubated with primary antibodies: goat anti-RAGE IgG (Millipore, CA, USA), rabbit polyclonal anti-AGEs IgG (Abcam, Cambridge, USA) or rabbit polyclonal anti-GLO-I IgG (GeneTex, CA, USA) (all diluted in 5% respective sera) in a humidified chamber at 4°C overnight. Sections were then incubated with biotinylated secondary antibodies: horse anti-goat IgG (- for RAGE and horse anti-rabbit IgG for AGEs and GLO-I (diluted in 5% respective sera) followed by avidin conjugated to HRP and finally

(Vector Laboratories, Peterborough, UK) SG chromogen (Vector Laboratories, Peterborough, UK).

Negative controls comprised substituting the primary antibody with non-immune immunoglobulin (Dako-Cytomation) in addition to thebiotinylated secondary antibodies as aboveand showed negative staining. To ensure comparability of immunostaining in each new experiment, sections from five cases immunostained in the previous experiment were re-stained and compared with the current experiment's results. Only when the five pairs of sections showed identical intensity of immunostaining the latest experiment was accepted, otherwise the entire run was repeated. Quantification of AGEs, RAGE and GLO-1 was performed semi-quantitatively using a light microscope under 400x magnification and identical light intensity[19]. The quantification of immunostaining was performed for skin epithelium, microvessels, and extracellular matrix. The intensity of immunostaining was assessed using a semi-quantitative method on a scale 0-5 where 0 is lack of immunostaining and 5 is the highest. Before commencing the semi-quantitative assessment, all sections were reviewed and the best representation of scores for each antigen in different skin structures was selected and used as a visual aid for the final assessment. All sections were blindly assessed three times in random sequence by the investigator (AA) to establish intra-observer repeatability. The sections were also assessed blindly by an expert pathologist (MJ) to establish inter-observer repeatability. The final results used for statistical assessment were reconciled scores between the two observers (AA & MJ).

Statistical analysis: Statistical analysis was performed using StatsDirect Version 2.7.7 (StatsDirect Ltd., Cheshire, UK) and SPSS 20.0 for Windows (SPSS, Chicago, IL) software. The data were assessed for normality using relevant histograms and Shapiro-Wilk test where appropriate. For normally distributed data, the results were expressed as mean±SD. Analysis of variance (ANOVA) was used to compare the means among the groups. Tukey test was used as a post hoc test to determine the significance of difference between pairs of groups. Non-normally distributed data were expressed as median (interquartile range). Kruskal-Wallis test was used to compare groups and Conover-Inman test was used as a post hoc test. Pearson correlation coefficient was used to assess correlations. Intra-observer and inter-observer repeatability was estimated using repeatability coefficient. $P<0.05$ was considered as statistically significant.

RESULTS

Clinical demographics (Table 1)

Age and duration of diabetes were well-matched between groups. HbA1c was higher in patients than controls ($P<0.001$) but was comparable between patients with and without neuropathy.

Table 1: Demographics and neuropathy assessment in control subjects and diabetic patients without with Diabetic Peripheral Neuropathy (DPN)

Variables	Control (n=30)	No DPN (n=46)	DPN (n=16)
Age(years)	42.55±15.63	42.31±12.94	46.79±11.6
Duration of Diabetes (years)		26.15±13.91	31.02±13.25
HbA1c (%)‡	5.36±1.13	8.11±1.16¶	8.7±1.86¶
IFCC (mmol/mol)‡	36.06±7.98	61.17±22.21¶	71.59±20.38¶
NSP (0-37)‡	0(0-0)	1(0-2) ¶	5(1-18) ¶§
McGill VAS 0-10)†	0(0-0)	0(0-0)	5(0-8) ¶§
NDS (0-10)‡	0(0-1)	2.5(0-4) ¶	6(4.5-8.5) ¶§
VPT (V)‡	6.2±6.03	7.88±5.73	27.05±14.01¶§
CT (°C)‡	28.3±2.03	26.78±2.95	15.84±11.87¶§
WT (°C)‡	36.7±2.22	38.78±3.41¶	44.52±4.7¶§
SA (uV)‡	20.34±8.68	12.17±6.79¶	3.98±3.69¶§
SNCV (m/s)‡	50.45±4.07	45.27±4.29	36.91±7.59¶§
PA (m/s)†	5.82±2.07	6.16±8.3	1.05±1.26¶§
PMNCV (m/s)‡	49.01±3.92	43.86±3.01¶	29.31±9.07¶§
DB-HRV (beats per min)†	34.13±13.45	34.17±18.24	17.54±15.39¶§
CNFD (no/mm^2)‡	37.85±5.83	28.65±6.76¶	16.7±8.24¶§
CNBD (no/mm^2)‡	94.67±37.34	62.39±29.08¶	33.43±22.9¶§
CNFL (mm/mm^2)‡	26.84±3.87	21.0±4.62¶	11.64±7.01¶§
IENFD (no/mm)‡	8.5±4.6	6.37±3.83¶	3.67±4.89¶§

Results are expressed as Mean ± SD or Median (interquartile range). Statistically significant differences using ANOVA or Kruskal Wallis test: † $P<0.01$, ‡ $P<0.001$, ¶ Post hoc (Tukey or Conover Inman test) results significantly different from control subjects, § Post hoc results significantly different from no neuropathy group. NSP (Neuropathy Symptom Profile); McGill VAS (McGill Visual Analogue Scale); NDS (Neuropathy Disability Score); VPT (Vibration Perception Threshold); CT (Cold Threshold); WT (Warm Threshold); DB-HRV (Deep Breathing- Heart Rate Variability); SA (Sural Amplitude); SNCV (Sural Nerve Conduction Velocity); PA (Peroneal Amplitude); PMNCV (Peroneal Motor Nerve Conduction Velocity), CNFD (Corneal Nerve Fibre Density); CNBD (Corneal Nerve Branch Density); CNFL (Corneal Nerve Fibre Length); IENFD (Intra-Epidermal Nerve Fibre Density).

Neuropathy Symptoms and Deficits

Neuropathy symptoms profile,McGill visual analogue and NDS were higherin patients than controls and were also higher in patients with DPN as compared to patients without DPN(P<0.001).

Quantitative Sensory Testing and Electrophysiology

VPT was increased in patients with neuropathy compared to controls (P<0.001) and those without neuropathy (P<0.001). CT was lower in patients with neuropathy compared with controls (P<0.001) and those without neuropathy (P<0.001). WT was higher in patients with (P<0.001) and without (P<0.001) neuropathy compared with controls and was also higher in patients without neuropathy compared to controls (P<0.001). SA was lower in patients with and without neuropathy (P<0.0001) compared to controls and was also lower in patients with compared to those without neuropathy (P<0.01). SNCV was lower in patients with neuropathy compared to controls (P<0.001) and patients without neuropathy (P<0.01). PA was lower in patients with neuropathy compared to controls (P<0.01) and patientswithout neuropathy (P<0.01). PMNCV was lower in patients with neuropathy compared to controls (P<0.001) and patients without neuropathy (P<0.001) and was also lower in patients without neuropathy compared to controls (P<0.01)

Small Fibre Testing

DB-HRV was lower in patients with neuropathy compared to controls (P<0.01) and those without neuropathy (P<0.01). CNFD, CNBD and CNFL were lower in patients with (P<0.001, P<0.001, P<0.001 respectively) and without (P<0.01, P<0.001, P<0.01 respectively) neuropathy compared to control subjects and were also significantly reduced in those with neuropathy compared to those without neuropathy (P<0.01, P<0.001, P<0.01 respectively). IENFD was lower in patients with (P<0.001) and without (P<0.01) neuropathy compared with controls and was also reduced in patients with neuropathy compared to those without neuropathy (P<0.01).

Intra-observer and Inter-observer repeatability

Intra-observer repeatability coefficients for epidermal immunohistochemistry scores of AGE, RAGE and GLO-I were 0.90, 0.87 and 0.85 respectively. Inter-observer repeatability coefficients for epidermal immunohistochemistry scores of AGE, RAGE and GLO-I were 0.88, 0.86 and 0.82 respectively.

Skin AGEs expression (Table 2, Fig. 1)

There was a significantly increased expression of AGEs in patients with neuropathy compared to controls and patients without neuropathy in the epidermis (P<0.001, P<0.01), microvessels (P<0.001, P<0.01), endothelium (P<0.001, P<0.05), basement membrane (P<0.01, P<0.01) and reticular ECM (P<0.01, P<0.01) respectively. AGEs expression was also significantly increased in diabetic patients without neuropathy compared to control subjects in the epidermis (P<0.01), endothelium (P<0.001) and reticular ECM (P<0.01)

Table 2: Skin AGEs expression in control subjects and diabetic patients without and with Diabetic Peripheral Neuropathy (DPN)

Skin structure	Controls	No DPN	DPN
N	30	46	16
Epidermis‡	2.06±0.70	2.47±0.73¶	3.33±1.20¶§
Microvessels ‡	2.27±0.76	2.44±0.78	3.21±0.94¶§
Endothelium‡	1.90±0.72	2.19±0.78¶	2.85±0.94¶§
Basement Membrane†	2.40±0.79	2.45±0.78	3.27±0.96¶§
Papillary ECM*	3.32±0.86	3.40±0.58	3.88±0.72¶
Reticular ECM †	2.80±0.86	3.07±0.71¶	3.79±0.71¶§

Results are expressed as Mean ± SD. Statistically significant differences using ANOVA: * P<0.05, † P<0.01, ‡ P<0.001, ¶ Post hoc (Tukey) results significantly different from control subjects, § Post hoc results significantly different from no neuropathy group. ECM (Extracellular Matrix)

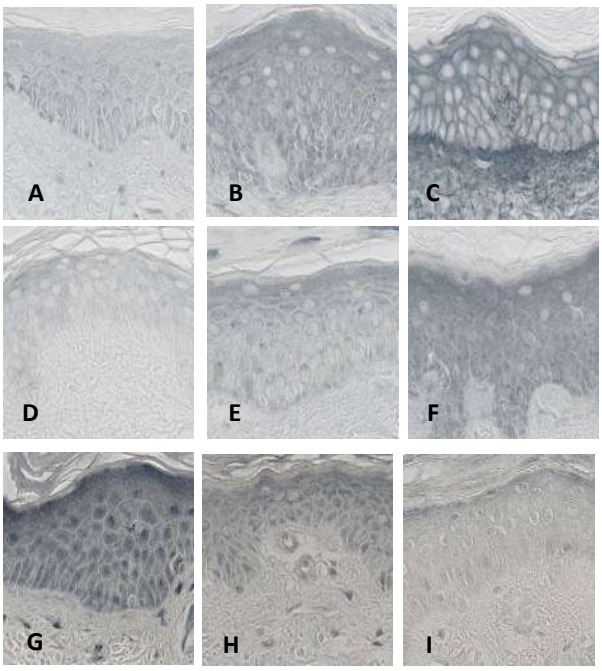

Fig. 1: Upper row: Immunolocalization of AGE in the epidermis (A-C) in control, diabetic patient without neuropathy and diabetic patient with neuropathy. Middle row: Immunolocalization of RAGE in the epidermis (A-C) in control, diabetic patient without neuropathy and diabetic patient with neuropathy. Lower row: Immunolocalization of GLO-I in the epidermis (G-I) in control, diabetic patient without neuropathy and diabetic patient with neuropathy.400x Maginification

Skin RAGE expression (Table 3, Fig. 1)

RAGE expression was significantly increased in patients with neuropathy compared to controls and patients without neuropathy in the epidermis (P<0.01, P<0.05), microvessels (P<0.001, P<0.05), endothelium (P<0.001, P<0.01) and basement membrane (P<0.001, P<0.05). RAGE expression was significantly increased in the epidermis (P<0.01) and microvessels (P<0.001) of those without neuropathy compared to control subjects.

Table 3: Skin RAGE expression in control subjects and diabetic patients without and with Diabetic Peripheral Neuropathy (DPN)

Skin structure	Controls	No DPN	DPN
N	30	46	16
Epidermis†	2.87±0.84	3.59±0.81¶	3.78±0.87¶§
Microvessels ‡	2.57±0.87	3.18±10¶	3.92±0.95¶§
Endothelium‡	2.55±0.77	3.09±0.98	3.90±0.91¶§
Basement Membrane‡	2.62±0.92	3.15±0.94	3.85±1.04¶§
Papillary ECM	2.87±0.94	3.19±0.96	3.33±0.72
Reticular ECM†	2.26±0.70	2.53±0.51	3.02±0.63¶

Results are expressed as Mean ± SD. Statistically significant differencesANOVA: † P<0.01, ‡ P<0.001, ¶ Post hoc (Tukey) results significantly different from control subjects, § Post hoc results significantly different from no neuropathy group. ECM (Extracellular Matrix).

Skin GLO1-I expression (Table 4, Fig. 1)

GLO-I expression was significantly reduced in patients with neuropathy compared to controls and patients without neuropathy in the epidermis (P<0.001, P<0.01), microvessels (P<0.001, P<0.01), endothelium (P<0.001, P<0.01) and basement membrane (P<0.001, P<0.01), respectively. There was also a reduction in GLO-I expression in the epidermis (P<0.001), microvessels (P<0.001), endothelium (P<0.001), basement membrane (P<0.001) and both papillary ECM (P<0.01 and reticular ECM (P<0.001) of patients without neuropathy compared to control subjects.

Table 4: Skin GLO-I expression in control subjects and diabetic patients without and with Diabetic Peripheral Neuropathy (DPN)

Skin structure	Controls	No DPN	DPN
N	30	46	16
Epidermis‡	3.69±0.83	3.10±0.82¶	2.73±0.88¶§
Microvessels‡	3.92±0.9	3.19±0.88¶	2.46±0.89¶§
Endothelium‡	3.88±10	3.10±0.99¶	2.47±0.65¶§
Basement Membrane‡	3.87±0.89	3.17±0.91¶	2.50±0.93¶§
Papillary ECM†	2.96±0.73	2.40±0.83¶	2.19±0.70¶
Reticular ECM ‡	2.98±0.83	2.50±0.8¶	2.09±0.47¶

Results are expressed as Mean ± SD. Statistically significant differencesANOVA:† P<0.01, ‡ P<0.001, ¶ Post hoc (Tukey) results significantly different from control subjects, § Post hoc results significantly different from no neuropathy group. ECM (Extracellular Matrix).

Correlation between skin AGEs expression and measures of neuropathy (Table 5)

There was a significant inverse correlation between skin AGEs expression in the epidermis and IENFD, CNFD, CNFL and SNCV. There was a significant inverse correlation between skin AGEs expression in the microvessels, endothelium and basement membrane with IENFD, CNFD, CNBD, CNFL, SA and SNCV. Papillary ECM AGEs expression correlated inversely with IENFD, CNFD and SA and reticular ECM expression correlated inversely with IENFD, CNFD, CNBD, CNFL and SA.

Table 5: Relationship between skin AGEs and measures of Diabetic Peripheral Neuropathy (DPN)

Skin structure	IENFD	CNFD	CNBD	CNFL	SA	SNCV
	r	r	r	r	r	r
	p	p	p	p	p	p
Epidermis	-0.634	-0.582	-0.209	-0.616	-0.205	-0.462
	0.000	0.000	0.119	0.000	0.149	0.000
Microvessels	-0.593	-0.546	-0.468	-0.666	-0.412	-0.531
	0.000	0.000	0.000	0.000	0.003	0.000
Endothelium	-0.561	-0.523	-0.609	-0.551	-0.402	-0.511
	0.000	0.000	0.000	0.000	0.003	0.000
Basement Membrane	-0.630	-0.434	-0.468	-0.527	-0.426	-0.532
	0.000	0.001	0.000	0.000	0.002	0.000
Papillary ECM	-0.467	-0.458	-0.161	-0.210	-0.408	-0.216
	0.000	0.000	0.231	0.117	0.003	0.116
Reticular ECM	-0.509	-0.442	-0.337	-0.504	-0.431	-0.168
	0.000	0.001	0.010	0.000	0.002	0.224

r- Pearson's correlation coefficient, significant correlations are in bold. ECM (Extracellular Matrix); IENFD (Intra-Epidermal Nerve Fibre Density); CNFD (Corneal Nerve Fibre Density); CNBD (Corneal Nerve Branch Density); CNFL (Corneal Nerve Fibre Length); SA (Sural Amplitude); SNCV (Sural Nerve Conduction Velocity)

Table 6: Relationship between skin RAGE and measures of Diabetic Peripheral Neuropathy (DPN)

Skin structure	IENFD	CNFD	CNBD	CNFL	SA	SNCV
	r	r	r	R	r	r
	p	p	p	P	p	p
Epidermis	-0.525	-0.591	-.0490	-0.560	-0.264	-0.512
	0.000	0.000	0.000	0.000	0.061	0.000
Microvessels	-0.568	-0.484	-0.517	-0.537	-0.474	-0.487
	0.000	0.000	0.000	0.000	0.000	0.000
Endothelium	-0.444	-0.547	-0.425	-0.528	-0.244	-0.523
	0.001	0.000	0.001	0.000	0.084	0.000
Basement Membrane	-0.504	-0.441	-0.267	-0.426	-.0494	-0.481
	0.000	0.001	0.044	0.001	0.000	0.000
Papillary ECM	-0.363	-0.425	-0.120	-0.140	-0.394	-0.217
	0.006	0.001	0.375	0.299	0.004	0.114
Reticular ECM	-0.408	-0.214	-0.020	-0.426	-0.186	-0.372
	0.002	0.121	0.882	0.001	0.190	0.006

r-Pearson's correlation coefficient, significant correlations are in bold. ECM (Extracellular Matrix); IENFD (Intra-Epidermal Nerve Fibre Density); CNFD (Corneal Nerve Fibre Density); CNBD (Corneal Nerve Branch Density); CNFL (Corneal Nerve Fibre Length); SA (Sural Amplitude); SNCV (Sural Nerve Conduction Velocity)

Table 7: Relationship between skin GLO-I and measures of Diabetic Peripheral Neuropathy (DPN)

Skin structure	**IENFD**	**CNFD**	**CNBD**	**CNFL**	**SA**	**SNCV**
	r	r	r	r	r	r
	p	p	p	p	p	p
Epidermis	0.464	0.482	0.252	0.503	0.408	0.491
	0.000	0.000	0.059	0.000	0.003	0.000
Microvessels	0.498	0.446	0.397	0.489	0.363	0.462
	0.000	0.000	0.002	0.000	0.009	0.000
Endothelium	0.442	0.464	0.356	0.502	0.311	0.456
	0.000	0.000	0.006	0.000	0.026	0.000
Basement Membrane	0.464	0.431	0.331	0.460	0.354	0.388
	0.000	0.001	0.012	0.000	0.011	0.003
Papillary ECM	0.228	0.238	0.119	0.351	0.145	0.382
	0.094	0.082	0.375	0.007	0.309	0.006
Reticular ECM	0.390	0.358	0.055	0.417	0.374	0.341
	0.003	0.007	0.684	0.001	0.007	0.015

r- Pearson's correlation coefficient, significant correlations are in bold. ECM (Extracellular Matrix); IENFD (Intra-Epidermal Nerve Fibre Density); CNFD (Corneal Nerve Fibre Density); CNBD (Corneal Nerve Branch Density); CNFL (Corneal Nerve Fibre Length); SA (Sural Amplitude); SNCV (Sural Nerve Conduction Velocity)

Correlation between skin RAGE expression and measures of neuropathy (Table 6)

There was a significant inverse correlation between skin RAGE expression in the epidermis and IENFD, CNFD, CBND, CNFL and SNCV. There was a significant inverse correlation between skin RAGE expression in the microvessels, endothelium and basement membrane with IENFD, CNFD, CNBD, CNFL, SA and SNCV. Papillary ECM RAGE expression correlated inversely with IENFD, CNFD and SA and reticular ECM expression correlated inversely with IENFD, CNFL and SNCV.

Correlation between skin GLO-I expression and measures of neuropathy (Table 7)

There was a significant direct correlation between skin GLO-I expression in the epidermis and IENFD, CNFD, CNFL, SA and SNCV. There was a significant direct correlation between skin GLO1 expression in the microvessels, endothelium and basement membrane with IENFD, CNFD, CNBD, CNFL, SA and SNCV. Papillary ECM GLO-I expression correlated with CNFL and SNCV and reticular ECM correlated inversely with IENFD, CNFD, CNFL, SA and SNCV.

DISCUSSION

This study is the first to report on the expression of the triplicate set of AGEs, RAGE and GLO-I in foot skin of type 1 diabetic patients and control subjects who had undergone detailed assessment of neuropathy. Skin AGEs expression was increased in patients with DPN in multiple skin structures, namely the epidermis, microvessels (endothelium and basement membrane) as well as the reticular ECM. Interestingly, skin AGEs expression was also moderately but significantly increased in patients without DPN

in the epidermis, endothelium and reticular ECM. Previous studies have shown increased expression of AGEs in skin collagen[20], nerves and blood vessels predominantly in animal models [21] compared to controls. Our findings therefore build on a robust link between AGEs and DPN in experimental diabetic neuropathy and indirect evidence from plasma levels of AGEs as well as skin autofluorescence[11,22]. In substudies of the Diabetes Control and Complications Trial (DCCT), AGEs were associated with DPN [23] and predicted the progression of microvascular complications, even after adjustment for HbA1c [8]. Glucospane, a major AGE has recently been proposed as a robust marker for diabetic microvascular complications including DPN [20]. Our findings suggest increased AGEs production as well as decreased detoxification in diabetic patients with DPN. Furthermore, we also show that this process is already operative in the early stages of neuropathy, in particular in relation to small fibre damage as evidenced by the correlation with IENFD and CCM abnormalities.

In combination with increased AGEs expression, we have also shown increased skin RAGE expression in patients without DPN and in particular those with DPN. In relation to the microvascular complications RAGE has been detected on epidermal nerves [19], peripheral nerves and their blood vessels [21], renal glomeruli and podocytes[24] and in the retina.[5] Therefore, our results provide translational support for previous reports showing increased RAGE expression in experimental DPN.[25] Moreover, in the same study RAGE knockout mice were protected against DPN. Recently, RAGE knockout diabetic mice exhibited enhanced post-injury nerve regeneration.[26] In the current study, AGEs and RAGE were co-localized in the same skin structures, which is in keeping with previous experimental reports demonstrating AGEs and RAGE co-localization.[21,27] The higher expression of RAGE suggests upregulation of the receptor in target structures, particularly in relation to the severity of DPN. Whether RAGE upregulation is a direct consequence of hyperglycemia, higher AGEs or other ligands, ROS, or a response to combined factors remains to be identified.

Emerging reports link the AGEs-detoxifying enzyme GLO-I, with diabetic microvascular complications, including DPN.[28] We show lower skin GLO-I expression in patients with DPN which was immunolocalized to the same structures where AGEs and RAGE expression were increased. Thus our data are consistent with recent studies which have related reducedGLO-I activity to DPN [4] including painful DPN.[10] Increased expression of GLO-I in the DRG of diabetic mice conveyed protection against small fibreloss.[4]Indeed GLO-I overexpression has been shown to reduce AGEs, RAGE, oxidative stress markers as well as increase mitochondrial oxidative phosphorylation[7]while under-expression generates the opposite effects.[28,29] GLO-I overexpressing mice were protected against IENFD loss.[4]This could also partially explain increased AGE expression as a consequence of reduced detoxification.

The combined data showing altered AGE/RAGE/GLO-I expression in the same skin structures and the significant correlations with measures of both large and small fibre neuropathy leads us to speculate that these three factors play a key mechanistic role in DPN. We also show significant correlations between the expression of AGE/RAGE/GLO-I in foot skin and both intraepidermal and corneal nerve fibre loss, which is comparable to or better than neurophysiology, adding to the data supporting the notion that CCM is a robust surrogate marker of DPN.

We acknowledge that due to the cross sectional nature of this study we can only provide association and not a cause effect relationship between AGEs/RAGE/GLO-I and DPN. Another limitation is the semi-quantitative nature of the scoring system, albeit we undertook rigorous blinded assessment with excellent reproducibility. Of course alternative techniques such as liquid chromatography/ mass spectrometry (LC/MS) could be used to interrogate the content of the biopsy material, however, this does not allow anatomical localization of AGEs/RAGE/GLO-I expression.

CONCLUSION

In conclusion, we report for the first time higher expression of AGEs/RAGE and lower expression of GLO-I in the foot skin of type 1 diabetic patients with DPN. Moreover, skin AGE/RAGE/GLO-I correlated significantly with small and large fibre damage. These findings suggest a potential role for AGE/RAGE/GLO-I as a marker and therapeutic target for DPN. Further clinicaland experimental studies are warranted to consolidate the evidence provided in this study.

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ORIGINAL ARTICLE

VARIABLES ASSOCIATED WITH KNEE OSTEOARTHRITIS IN A TERTIARY CARE HOSPITAL OF TAMILNADU, INDIA

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ABSTRACT

Introduction: Osteoarthritis (OA) is a chronic degenerative disorder of multifactorial etiology characterized by loss of articular cartilage, hypertrophy of bone at the margins, subchondral sclerosis and range of biochemical and morphological alterations of the synovial membrane and joint capsule. Osteoarthritis (OA) is the second most common rheumatological problem and is most frequent joint disease with prevalence of 22% to 39% in India.

Methodology: A cross sectional study, done in 3 private hospitals of Tamilnadu. Total 135 patients interviewed after taking informed written consent. Questions pertaining to their physical activities, symptoms experienced, postures etc. were asked.

Results: Maximum numbers of patients were from age group of 61 to 70 years (37.04%). It was followed by age group of 51 to 60 years (29.63%).There were 91 (67.41%) female patients in the study group. Only 12 (8.89%) patient were illiterate. Maximum numbers of patients have completed their secondary schooling. As there was female predominance, we found 52 (38.52%) patients were house wife. Where as 22 (16.30%) patients were laborer. BMI was an important correlates of OA as 79 (58.52%) patients were obese. It was observed that OA patients were using Squatting and Cross legged positions in day to day activities like Job work, Food Preparation, Sweeping and Moping.Most common symptom was Usage related pain (42.22%) and persistent pain (27.41%). Most common sign was crepitus and it was followed by bony enlargement.

Conclusion: Present study shows that age group of 61 to 70 years is the most common age group for OA of knee. Study also shows predominance of female gender. Overweight and Obesity are one of the most common risk factors. Patients using Indian style toilets, having squatting crossed leg position and bending position in day to day activities are more commonly affected. Most common symptom is Usage related pain followed by persistent pain. Most common sign is crepitus and it was followed by bony enlargement.

Keywords: Osteoarthritis, Knee, Squatting position, Crepitus

INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative disorder of multifactorial etiology characterized by loss of articular cartilage, hypertrophy of bone at the margins, subchondral sclerosis and range of biochemical and morphological alterations of the synovial membrane and joint capsule.Pathological changes in the late stage of OA include softening, ulceration and focal are integration of the articular cartilage; synovial inflammation also may occur. Typical clinical symptoms are pain, particularly after prolonged activity and weight bearing; whereas stiffness is experienced after inactivity. It is probably not a single disease but represents the final end result of various disorders as joint failure. It is also known as degenerative arthritis, which commonly affects the hands, feet, spine, and large weightbearing joints, such as the hips and knees.Most cases of osteoarthritis have no known cause and are referred to as primary osteoarthritis. Primary osteoarthritis is mostly related to aging. It can present as localized, generalized or as erosive osteoarthritis. Secondary osteoarthritis is caused by another disease or condition.

Global statistics reveals over 100 million people worldwide suffer from OA, which is one of the most common causes of disability. [1,2]Globally, OA is the eighth leading cause of disability with the joint most frequently associated with disability being the knee.[3]

Epidemiological profile of this disease in India is not clear but it is estimated that osteoarthritis (OA) is the second most common rheumatological problem and is most frequent joint disease with prevalence of

22% to 39% in India.[4]Prevalence of OA in India is reported to be in the range of 17 to 60.6%.[5]The reported prevalence of OA from a study in rural India is 5.78%.[6]

The irreversible nature of disease and increasing prevalence of OA in developing countries is major concern. The longeitivity of population is increasing in India which is major concern for age related disability the difficulty in movements, pain, stiffness of joints are common symptoms of OA. Therefore it depends mainly on prevention of modifiable risk factors to preserve at ease movement in elderly population.

Therefore, for finding out the current burden of Osteoarthritis and its association with lifestyle related factors, it was essential to undertake such a study on Prevalence of Knee Osteoarthritis.

METHODOLOGY

The present study was a Cross sectional Study conducted in 3 private hospitals Tamilnadu. All patients attending Orthopedic OPD department forms the study population. All patients attending Orthopedic OPD from December 2014 to November 2015 anddiagnosed withPrimary Osteoarthritis of Knee were enrolled in the study. Informed written consent in local language was taken. Those who were not willing to give consent were excluded from the study without affecting their due course of treatment. All reportsand related medical records of all patients were obtained. A pre-tested semi structured questionnaire was administered to all patients.Questionnaire was divided broadly in to two parts.

The first part included socio-demographic details. The second part consisted of the possible risk factors for developing OA of the knee such as age, gender, occupation, family history of OA, physical activity, history of injury to the knee etc.

The questionnaire was validated by translation into the local language and reviewed by a group of experts. It was subsequently piloted among a small group of individuals to test their comprehension and suitable changes were made accordingly.

X-ray, Weight and Height measurement along with all necessary investigations according to standard protocol were done. Study was approved by Institutional Ethical Committee of the institute.

Confidentiality of data was maintained at all level of the project. The data was coded and entered into Microsoft Excel and analyzed using standard statistical software package Epi info v3.5.1 for proportions, frequencies, and associations.

RESULTS

There were total 158 patients diagnosed with Osteoarthritis (OA) of knee during study period. Out of these, 23 patients refuse to participate in the study. Thus, total 135 patients enrolled in the study.

Table 1 shows basic socio-demographic characteristics of patients. Maximum numbers of patients were from age group of 61 to 70 years (37.04%). It was followed by age group of 51 to 60 years (29.63%).

Table 1: Basic Profile of patients with Knee OA

Characteristics	Patients (N=135) (%)
Age	
<40	5 (3.70)
41-45	12 (8.89)
46-50	19 (14.07)
51-55	23 (17.04)
56-60	17 (12.59)
61-65	29 (21.48)
66-70	21 (15.56)
>70	9 (6.67)
Gender	
Male	44 (32.59)
Female	91 (67.41)
Educational Status	
Illiterate	12 (8.89)
Just Literate	9 (6.67)
Primary School	18 (13.33)
Secondary School	44 (32.59)
Higher Secondary School	15 (11.11)
Graduate	23 (17.04)
Post Graduate	14 (10.37)
Occupation	
Professional	16 (11.85)
Semi-professional	12 (8.89)
Shop/Farm Owner	8 (5.93)
Skilled worker	9 (6.67)
Semiskilled Worker	16 (11.85)
Labourer	22 (16.30)
Housewife	52 (38.52)
BMI	
Underweight	3 (2.22)
Normal	8 (5.93)
Overweight	45 (33.33)
Obese	79 (58.52)
Physical Activity	
Sedentary	46 (34.07)
Moderate	63 (46.67)
Strenuous	26 (19.26)
Type of Toilet	
Indian	105 (77.78)
Western	14 (10.37)
Both	16 (11.85)

Data shows predominance of female gender. There were 91 (67.41%) female patients in the study group. As our study was done in multispeciality hospital of Urban area, more educated people were found in the study. Only 12 (8.89%) patient were illiterate. Maximum numbers of patients have completed their secondary schooling.

Table 2: Relation of Posture during common day to day activity with OA

Type of Work	Posture during work No. (%)					
	Squatting	Cross legged	Kneeling	Bending	Prolonged Standing	Sitting on chair
Job Work	56 (41.48)	48 (35.56)	23 (17.04)	62 (45.93)	16 (11.85)	12 (8.89)
Food preparation	50 (37.04)	47 (34.81)	16 (11.85)	15 (11.11)	32 (23.70)	39 (28.89)
Sweeping	46 (34.07)	0	18 (13.33)	55 (40.74)	0	39 (28.89)
Moping	39 (28.89)	0	6 (4.44)	22 (16.30)	37 (27.41)	39 (28.89)

As there was female predominance, we found 52 (38.52%) patients were house wife. Where as, 22 (16.30%) patients were laborer. BMI was an important correlates of OA as 79 (58.52%) patients were obese. Overweight patients contribute 33.33% out of total 135 patients. Type of toilet was also correlates with OA of knee. Out of total 135 patients of Knee OA, 105 (77.78%) patients were using Indian toilet.

Table 2 shows different postures OA patients were using during day to day activities. It was observed that OA patients were using Squatting and Cross legged positions in day to day activities like Job work, Food Preparation, Sweeping and Moping.

Table 3: Common signs and symptoms of patients

Variables	No. (%)
Symptoms	
Persistent knee pain	37 (27.41)
Usage related pain	57 (42.22)
Feeling of giving away	14 (10.37)
Morning stiffness	15 (11.11)
Rest and night pain	4 (2.96)
Signs	
Crepitus	41 (30.37)
Bony enlargement	12 (8.89)
Warmness around knee	6 (4.44)
Redness around knee	7 (5.19)
Periarticular tenderness	12 (8.89)
Limited movement	8 (5.93)
Effusion	4 (2.96)

Table 3 shows common symptoms and signs of patients of OA of knee. Most common symptom was Usage related pain (42.22%) and persistent pain (27.41%). Most common sign was crepitus and it was followed by bony enlargement.

DISCUSSION

With the aim of finding factors associated with Osteoarthritis of knee, we had interviewed 135 OA knee patients.

In compliance with the previous studies, a higher prevalence of OA with increasing age has been noted.[7]We found that maximum number of patients were from age group of 61 to 70 years (37.04%). It was followed by age group of 51 to 60 years (29.63%). In a study done in Jammu and Kashmir, one third of the population above the age of 65 was found to have OA.[8]More than half of those with arthritis are under 65 years of age. Nearly 60% of Americans with arthritis are women. Indian data in this regard is lacking. It is difficult to estimate the prevalence of osteoarthritis because there are no universally applicable criteria for its diagnosis. Radiographic and symptomatic knee OA in adults 45 years or older was prevalent in 19% and 7% of Framingham subjects, respectively, and in 28% and 17% of Johnston county subjects, respectively.[9]

Many studies had also found that the overall number of US adults affected by OA in any joint clearly has increased during recent decades due to aging of the population and the increasing prevalence of obesity.[10]Thus, age is the most powerful risk-factor for OA. [11]The prevalence of knee OA increases with age [12]; therefore, the impact of this disease will become even more substantial with the aging of the population. Studies have shown that knee OA greatly diminishes health status in the elderly. [13]Studies shows that not only was there a marked increase in the occurrence of severe OA with advancing age, but that this age-related increase appeared to be exponential after 50 years of age.[14]A study on prescribing patterns in the management of arthritis in the department of orthopaedics, the study reveals that out of 75 osteoarthritis patients, about 60% are in the age group between 51-65 years. [15]

In our study, there were 91 (67.41%) female patients in the study group.The Framingham Knee Osteoarthritis study suggests that knee osteoarthritis increases in prevalence throughout the elderly years, more so in women than in men.[16]Females are found to have more severe OA, more number of joints are involved, and have more symptoms and increased hand and knee OA.[17]These observations and others reporting a painful form of hand osteoarthritis after the menopause suggest that loss of estrogen at the time of menopause increases a woman's risk of getting osteoarthritis,[18] Obesity preceeds rather than follow knee osteoarthritis and indeed weight loss prevents development of knee osteoarthritis.[19]

Various studies reveal that, being overweight is a clear risk factor for developing Osteoarthritis. Population-based studies have consistently shown a link between overweight or obesity and knee OA. Esti-

mating prevalence across populations is difficult since definitions for obesity and knee OA vary among investigators. Data from the first National Health and Nutrition Examination Survey (HANES I) indicated that obese women had nearly 4 times the risk of knee OA as compared with non-obese women; for obese men, the risk was nearly 5 times greater.[20]In lifestyle such as weight reduction and exercise. Weight reduction is quite effective and recommended for overweight or obese patients especially in symptomatic knee OA. It reduces the pain and improves physical function. It can be accomplished through an intensive low calorie diet programme. These lifestyle changes must be continued throughout life.[21]

The occupational physical activities which including monotonous motions and great forces such as kneeling, squatting on joints , climbing, and heavy lifting. [22]Clinically, the condition is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of local inflammation.[23]

Pain is the first and predominant symptom, causing loss of ability and often stiffness.Pain is generally described as a sharp ache, or a burning sensation in the associated muscles and tendons. The pain is intermittent and is worse with use and better with rest. The stiffness generally improves after 30 minutes of activity unlike the prolonged (usually > 30 min) stiffness caused by rheumatoid arthritis. OA of the knee can cause a crackling noise called crepitus, when the affected joint is moved or touched, and patients may experience muscle spasm and contractions in the tendons. We found in our study that most common symptom was Usage related pain (42.22%) and persistent pain (27.41%). Most common sign was crepitus and it was followed by bony enlargement.Occasionally, the patient presents with swelling or joint effusion sometimes calledwater in the knee in lay terms due to fluid within the joint.

CONCLUSION

Present study shows that age group of 61 to 70 years is the most common age group for OA of knee. Study also shows predominance of female gender. Overweight and Obesity are one of the most common risk factors. Patients using Indian style toilets, having squatting crossed leg position and bending position in day to day activities are more commonly affected. Most common symptom is Usage related pain followed by persistent pain. Most common sign is crepitus and it was followed by bony enlargement.

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ORIGINAL ARTICLE

SAFETY OF LAPRASCOPIC TUBAL LIGATION IN PATIENTS WITH PREVIOUS CASAREAN SECTION

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ABSTRACT

Aims: To evaluate the technique of laparoscopic tubal sterilization in patients with previous caesarean section with respect to age, parity, technical difficulty, operative time, intra-postoperative comfort and its suitability for mass sterilization camps.

Methods: A prospective study of laparoscopic tubal ligation done at teaching Medical College and in camp from August 2010 to August 2011. Total 70 cases were operated under intramuscular sedation (Pentazocine and Promethazine) and local anesthesia (inj xylocaine). Operations were performed in interval and post-abortal cases. Data were analyzed with respect to age, parity, technical difficulty, operative time, intra/postoperative complication and postoperative comfort.

Result: Most of the patients were in age group of 20-30 indicating long post-TL period. Most of the patients were having two children. Adhesions were present in 15.7% and difficulties in getting tube were present in 5.7% and TL was not possible in one (1.4%) patient. Most of the patients were comfortable in postoperative period within 24 hours.

Conclusion: Laparoscopic tubal ligation is possible in previous caeserean with minimal risk and devoid of complication. It also requires further study and follow up to comment on the failure rates.

Key words: Lap TL, Casarean Section, Adhesion, Pffanenstial Scar

INTRODUCTION

Female sterilization is a surgical procedure used to end woman's ability to become pregnant. This procedure involves ligation with or without resection or blocking of both the fallopian tubes so that egg and sperm can not meet.

Amongst the major health problems in India, population explosion ranks first. In developing countries over 70% of all sterilization is done in women.[1] But the popularity and success of TL program largely depends upon the success of its reversal. Female sterilization is the most widely used contraceptive in India. Female sterilization by laparoscopic method came up in the National Family Planning programs in India.[2,3] The most common surgery of reproductive age group is caesearean section and the patients included in study are multigravida; so patients with previous one or more caesearean sections are included in this study. Due to previous surgery, the intra-abdominal mileu can be challenging during laprascopy.[4-8] We have specifically studied this subset and evaluated the safety of Lap TL without much morbidity.

METHODOLOGY

Patients having one or more LSCS and desiring for lap TL were selected. All patients were in the first ten days of menstrual cycle. Patients were selected under national tubal ligation programme. They all met basic criteria of haemoglobin >8 gm/dl and urine sugar absent. HIV testing and urine pregnancy test were also done to rue out pregnancy.They had undergone procedure under local anesthesia and intramuscular sedation. We followed a routine of giving Inj. Fortwin I/M (Pentazoine 20mg), Inj Phenergan I/M (Promethazine 50mg) and Inj Atropine I/M (1mg); Inj Tetanus toxoid half an hour before the procedure was given in our centre.

Patients were taken to Operation Theater and given 45 degree trendlenberg position. Painting and draping was done. 3cc Xylocaine 2% was injected below umbilicus; small infra-umbilicus skin incision was given with 11 no knife. Trocar canula with valve open was introduced in direction of pelvis without pneumoperitonium. Hissing sound of air on lifting of abdomen confirmed that cannula is intraperitoneal. Laprogator with ring applicator was introduced and

after confirming the intra peritoneum, pneumoperitonium was created with atmospheric air. Fallopian Tubes were identified and confirmed and ring were applied over isthmic ampullary junction region in avascular area. If omental adhesions were present then window made in avascular area and then tubes were reached. In some cases vaginal manipulation of uterus was required.

All patients were given discharge on the same day after 5 hours of procedure with oral antibiotic. Stitch removal was done on the seventh day.

RESULTS

Factors of age, parity, number of previous cesarean section, type of scar on abdomen, stay in hospital, and intra and postoperative complications were analyzed. Age ranged from 20 to 35 years and maximum patients (80%) were in 25-29 years age group.

Table 1: Age and Parity wise distribution of Participants

Age/Parity	P2	P3	Total
20-24	18 (30)	1 (10)	19 (27.14)
25-29	32 (53.33)	5 (50)	37 (52.86)
30-34	8 (13.33)	4 (40)	12 (17.14)
>35	2 (3.33)	0 (0)	2 (2.86)
Total	60 (100)	10 (100)	70 (100)

Sixty patients underwent Lap TL after two deliveries. 54 of them had previous two LSCS. The rest 10 patients underwent LAP TL after three deliveries. Amongst these, 2 had previous 3 LSCS, 6 had previous two LSCS and 2 had one LSCS. 54 patients having two LSCS and 14 patients having one LSCS and two patients having three LSCS. 60 patients had pfannestial skin incision and 10 patients had vertical incisions.Local anesthesia with intramuscular sedation was used in all 70 patients.

Table 2: Relation between Parity, Number of LSCS and Type of Scar

Type of Scar	One LSCS		Two LSCS		Three LSCS	
	Vertical	Pffanenstial	Vertical	Pffanenstial	Vertical	Pffanenstial
P2	2	10	7	41	0	0
P3	0	2	1	5	0	2
Total		14		54		2

Intra-operative complication: 6 patients out of 20 patients having vertical scar had adhesion over scar line and two patients had severe adhesion of omentum in which window made in avascular area and then reached to the tube. 5 patients out of 50 patients having pfannestial scar had adhesion out of them one had severe adhesion so require window in omentum and TL was done and in one patient both tubes were totally covered with omentum and so TL was not possible.

Table 3: Complications with Type of scar

	Adhesion (%)	Difficulty in Getting Tube (%)	Tl Not Possible (%)
Vertical Scar	6 (8.5)	2 (2.85)	-
Pffanenstial Scar	5 (7.0)	2 (2.85)	1 (1.4)
Total	11 (15.7)	4 (5.7)	1 (1.4)

Postoperative complication: No obvious postoperative complications were reported.

Stay in hospital: Average stay in hospital was six hours and all patients were discharged with oral antibiotic and analgesic. Stitch removal was done on the seventh day. There were no wound related problems.

DISCUSSION

In our study most of the patients undergoingTL were in age group of 20-30 (80%) and 60 patients (86%) underwent TL after having two delivery while 10 patients (14%) underwent TL after three delivery. Out of 70 patients 14 (20%) patients had one lscs 54 (77%) had two LSCS and 2 (3%) had three LSCS. 50 (71%) had pffanestial scar and 20 (29%) had vertical scar.

CONCLUSION:

Technique of lap TL in previous LSCS was found to be easy to perform and with mild risk and devoid of complication of open TL[4,8] Laparoscopy provides an opportunity to inspect the abdominal and pelvic organs, requires small incisions, is immediately effective, and enables a rapid return to full activity. [5,6,7] Caesarean section methods have refined leading to wider exposure even at primary level. There are fewer intraoperative and long term complications reported. Meticulous training and widespread availability of laprasopy units have made TL in such subsets a preferred method in all the centres handling such patients.[9,10] Practical aspects must be taken into account before implementing endoscopic techniques in settings with limited resources.[8,11,12]. Tubal occlusion by laparoscopy is a safe and effective method of permanent contraception.[1,5]

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ORIGINAL ARTICLE

CHRONIC KIDNEY DISEASE AND RISK FACTOR PREVALENCE IN DEHRADUN DISTRICT

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ABSTRACT

Objectives: The study was conducted to assess the prevalence of risk factors for Chronic Kidney Disease and to find out the prevalence of CKD.

Methodology: A community based survey was conducted in the selected urban wards of the district Dehradun to collect the required information of the study. Individuals aged between 40 – 80 years, residents of the area for at least one year were included in the study. Information regarding number of households and population in each ward was obtained. They were informed about the purpose of study. The household in each ward was selected on PPS basis. Out of each selected household, study subject (40-80yrs) was drawn on the basis of "Kish" method basis. After obtaining the written informed consent, they were interviewed using the WHO (stepwise approach for NCDs) questionnaire and SCORED screening test tool to identify risk factors. The subjects who were at risk were screened for chronic kidney disease. The data was compiled, entered & analyzed using SPSS version 19.

Results: Raised BP, diabetes and cases of heart attack were more among males as compared to females. The prevalence of CKD was 2.1 percent. Proportion of CKD cases was almost same in both sexes. Chronic kidney disease prevalence was 1.1%, 5.1% and 8.2% in 50-59, 60-69 and >70 year age groups.

Conclusion: The prevalence of diseases like hypertension, diabetes was high in the urban population etc. The disease prevalence tends to increase with the advancing age.

Key words: Chronic Kidney Disease, risk factors, prevalence

INTRODUCTION

The economic development and changing lifestyle habits are posing a significant impact on the public health scenario. The increased prevalence of non communicable diseases and their risk factors are becoming a matter of worry. The climbing burden of lifestyle related disorders is likely to raise the burden on already limited resources of health sector. One such condition battling in India and other nations is increased prevalence of Chronic Kidney Disease (CKD) which is considered as a silent epidemic of 21st century.

The prevalence of CKD is estimated to be 8-16% worldwide.[1] The prevalence in Asia is not lower than that seen in Western countries. In the absence of a proper registry and paucity of population-based studies, exact prevalence of CKD in India is not known. Based on data from major tertiary care centers, the presumptive estimates of incidence of End Stage Renal Disease in India are 100 per million populations.[2] It is obvious that in a country like India, screening the whole population for CKD is neither required nor feassible. Thus, we need to concentrate on screening individuals at high-risk (e.g. people older than 50 years; people with a history of diabetes mellitus, hypertension, cardiovascular disease; or who have a family history of CKD) for CKD. The early detection of high-risk individuals is critical for both the development and implementation of strategies to prevent the progression to ESRD. Progress to kidney failure or other adverse outcomes could be prevented or delayed by early detection and treatment with population based screening.

Thus a community based study was conducted in the urban area of district Dehradun with the aim to determine, among at risk in general population, the prevalence of risk factors for Chronic Kidney Disease and the prevalence and association of risk factors in individuals with CKD

METHODOLOGY

The present study was conducted and sample size of 3300 was drawn from the prevalence of 12.3 % (According to study conducted in South India).[3] A community based survey was conducted in the se-

lected urban wards of the district Dehradun to collect the required information of the study. Individuals aged between 40 – 80 years, residents of the area for at least one year were included in the study. Information regarding number of households and population in each ward was obtained. They were informed about the purpose of study. The household in each ward was selected on PPS basis. Out of each selected household, study subject (40-80yrs) was drawn on the basis of "Kish" method basis so that in each age group, appropriate number of subjects had been acquired. If the eligible subject was not present, next eligible subject was chosen. While interviewing female subjects, presence of another female was ensured. All the subjects in the household were informed about the purpose of study. After obtaining the written informed consent, they were interviewed using the WHO (stepwise approach for NCDs) questionnaire and SCORED screening test tool to identify risk factors.

Random selection of the Nagarpalika

⇩

Random selection of the ward (20%)

⇩

Selection of household (randomly on PPS basis)

⇩

Selection of study subject (using Kish method)

⇩

WHO stepwise approach and SCORED

⇩

If risk factor score > 4, testing for proteinuria

⇩

If two readings of proteinuria 1 week apart positive, Serum creatinine estimated

⇩

If serum creatinine >1.2mg/dl subject labeled as CKD

Scoring was done by applying "SCORED" questionnaire. If total score of 4 or more was obtained, the urine sample of subjects was analyzed for presence of urine protein. The subjects were informed a day before to keep the morning sample of urine in a sterilized bottle and the sample was checked for protein. If the sample was positive for 100mg/dL or more, then the test was repeated after one week. The samples which were positive second time also were investigated for serum creatinine. If serum creatinine was more than 1.2 mg/dl, then the subjects were labeled as cases of chronic kidney disease. During the course of study, constant supervision was done in order to ensure quality work. Collected data was compiled, tabulated and analyzed by using SPSS version 19.0 software and Microsoft Excel 2007. Percentages were calculated for all the variables, Chi square was applied for categorical variables to show the association. Graphs were made using Microsoft Excel version 2007. Significant level was assumed at $p<0.05$.

RESULTS

The present study was conducted for a period of one year. A total sample size of 3300 was taken based on the prevalence of CKD according to a study in South India. Total study subjects were 3304. Out of this, 1178 were males and 2126 were females. There were 1195 subjects in 40-49 year age group, 984 in 50-59, 729 in 60-69, and 396 in 70-80 year age group. Table 1 depicts the prevalence of the chronic kidney disease risk factors as per SCORED screening test tool.

Table 1: Prevalence of risk factors for CKD according to SCORED screening test tool

Variable	Male (%)	Female (%)
Age 50-59	338 (28.7)	646 (30.4)
Age 60-69	268 (22.7)	461 (21.7)
Age >70	191 (16.2)	205 (9.6)
Female	00	2126 (100)
Anemia	92 (7.8)	246 (11.6)
High B.P.	652 (55.3)	699 (32.8)
Diabetic	426 (36.1)	860 (26)
H/O Heart attack	100 (8.4)	50 (2.3)
CHF	36 (3.1)	79 (3.7)
Circulation disease	18 (1.5)	4 (0.2)
Protein in urine	34 (2.9)	59 (2.8)

Table 2: Prevalence of subjects at risk for chronic kidney disease (according to SCORED tool)

Risk factor Score	Male (%) (n=1178)	Female (%) (n=2126)	Total (%) (N= 3304)
< 4	630 (53.5)	1172 (55.1)	1802 (54.5)
≥ 4	548 (46.5)	954 (44.9)	1502 (45.5)

$\chi_{(1)}^2 = 0.829$; $p > 0.05$

Table 3: Prevalence of Chronic Kidney Disease

	CKD present	CKD absent
Overall subjects (3304)	2.1%	97.9%
At risk subjects (1502)	4.5%	95.5%

Table 4: Distribution of at risk population according to sex andchronic kidney disease

	CKD present	CKD absent
Males	4.2%	95.8%
Females	4.7%	95.3%

($\chi^2=0.058$; $p > 0.05$)

The table 2 depicts the number of males and females having risk factors according to SCORED screening

test tool. Out of the total 3304 subjects, 45.5% i.e. 1502 were having 4 or more risk factors present. Total of 548 males (46.5% subjects) had high score of risk factors. Females were also nearly in same proportion (44.9%).This was however not statistically significant.

Table 5: Prevalence of Chronic Kidney Disease among various age groups (at risk)

Age	CKD prevalence
40-49 yrs	0%
50-59 yrs	1.10%
60-69 yrs	5.10%
70-80 yrs	8.20%

($\chi_{(3)}^2 = 112.516$; $p < 0.0001$)

Table 3 shows the prevalence of chronic kidney disease. Out of the total survey population i.e. 3304, 2.1% (68 subjects) of the population were found to have CKD. Among the subjects who were at risk according to the SCORED screening test tool, about 4.5% subjects had CKD.

Table 4 shows the prevalence of CKD, according to gender, in the population who is at risk (According to SCORED test tool). Among at risk population, more females (4.7%) were found to have CKD as compared to 4.2% of the males.

Table 5 shows that the advancing age having direct relation with CKD. No case of CKD was diagnosed in the 40-49yr age group. Maximum cases (8.2%) were in 70-80yr age group followed by 5.1% in 60-69 year age group and 1.1% of the subjects in 50-59yr age group. This was highly significant statistically.

DISCUSSION

Global studies have revealed that the emergence of chronic kidney disease as a silent pandemic. CKD usually gets unnoticed as the symptoms appear late when enough damage has already occurred. This study explores the prevalence of CKD and its risk factors using the data from urban areas of Dehradun.

The current study showed overall 2.1% prevalence of chronic kidney disease (2% males and 2.2%females). A similar study by Agarwal *et al* studied south Delhi in 2005 in urban population and reported stage 3 prevalence of 0.785%.[4] The prevalence was low because the cut off for serum creatinine was very high (more than 1.8 mg/dL). Study by Narinder P Singh et al in Delhi (2005-07) on the basis of proteinuria and reduced eGFR reported the prevalence of stage 3 CKD to be 4.2%.[5]

In our study prevalence of CKD was nearly equal in males and females (2% in males and 2.2% in females). Singh in a study in Delhi also showed that there was no difference in prevalence of CKD on the basis of gender.[5] However beyond 60 years of age, females had higher prevalence (5.76% vs. 3.46%).

This study showed the trend of increasing prevalence of CKD with the advancing age. Prevalence among the at risk subjects of the age group 50-59 was 1%; 60-69 year age group was 5.1% and 70-80 year age group was 7.6%. The SEEK-India cohort study also showed higher prevalence in the older age group.[6] Venkatachalam J in Tamil Nadu showed that prevalence of CKD in the age group 60 years and above was 19.8% against the overall 12.3%.[3] Narinder Singh in his study in Delhi found that the prevalence of CKD was increasing with age.[5]

CONCLUSION AND RECOMMENDATIONS

Changes in the lifestyle and habits of urban population lead to increase in prevalence of the risk factors for NCDs. Further, these make a major contribution to association with chronic kidney disease. The cost of treatment is very high for CKD. Thus a healthy lifestyle needs to be adopted to prevent CKD. Specific prevention strategies which reduce exposure to risk factors should be applied. Physical activity plays a major role in preventing chronic kidney disease. Advice should be given for healthy home available diet with low consumption of fat, salt and sugar and more consumption of fresh fruits, vegetables, and dietary fiber etc.

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ORIGINAL ARTICLE

ROLE OF INTRAVITREAL BEVACIZUMAB INJECTION FOR MANAGEMENT OF NEOVASCULAR AGE RELATED MACULAR DEGENERATION

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ABSTRACT

Background: Age related macular degeneration (ARMD) is the major cause of severe visual loss in older adults.Different treatment modalities are available such as: Laser photocoagulation,photodynamic therapy,transpupillary thermotherapy,submacular surgery & anti-vegf.

Aims & Objectives: The aim of our study was to evaluate the efficacy and safety of intravitreally administered Bevacizumab a humanized monoclonal anti –VEGF in Neovascular Age related Macular Degeneration.

Methodology: This non randomized, prospective study was carried out on 75 eyes of 75 patients attending the OPD at M & J Institute Of Ophthalmology and diagnosed as having Neovascular ARMD confirmed on FFA and SD-OCT . After taking written informed consent all patients were injected with intravitreal Bevacizumab 1.25 mg/0.05 ml. Follow up visits were scheduled one week, one month postprocedure and every monthly thereafter.

Results: 75 eyes of 75 patients were included in this non randomized prospective study. & 29.33% patients required 2 injections. Visual acuity is improved more than 3 lines from baseline in 21.33% patient, 64% patient have 2-3 lines gain & 6.66% patients showed 0-1 line gain in snellen's visual acuity. 5.33% patients have a loss of 1 line from baseline & 2.66% patients showed loss of 2-3 lines. Central foveal thickness decreased more than 200 microns from baseline in 52% patients, 28% patients have decreased of 100-200 microns & 20% patients have decreased of less than 100 microns.

Discussion: Approximately 10 % of ARMD patients manifest the neovascular form of the disease. 12 weeks). Our study showed that 80% patients had decrease in central foveal thickness more than 100 microns from baseline at the end of one year. 85% patients had gain of 2 or more lines on Snellen's visual acuity chart from baseline.No patient had any serious local or systemic adverse reactions.Limitations of our study is small number of patients,ICG not done,not compared with other anti-vegf drugs.

Conclusion: Intravitreal Bevacizumab is a safe and effective drug in treatment of neovascular age related macular degeneration without any serious systemic or local adverse effects

Key words: Age related macular degeneration, intravitreal injection, bevacizumab

INTRODUCTION

Age related macular degeneration (ARMD) is the major cause of severe visual loss in older adults. The prevalence in India varies from 0.6% to 2.7% in south India to 4.7% in north India. Most ARMD patients have dry form of disease consisting of macular drusen or RPE abnormalities or both. Approximately 10% of ARMD patients manifest the neovascular form of the disease.

Neovascular ARMD includes choroidal neovascularization & associated manifestation such as pigment epithelial detachment & retinal pigment epithelial tears, disciform scarring & vitreous hemorrhage.[1]

CNVM appears as a neovascular sprout growing under or through the RPE through breaks in bruchs membrane. These vessels proliferate between rpe & bruchs & leak fluid in all retinal layers. Choroidal neovascularization appears as a grey elevation deep to the retina with overlying neurosensory detachment. The diagnosis is confirmed by fluorescein angiography, indocyanine green angiography & optical coherence tomography.[2]

Different treatment modalities are available such as: 1). Laser photocoagulation- useful in extrafoveal or juxtafoveal cnv with well defined margins. 2). photodynamic therapy- useful in subfoveal, juxtafoveal cnv 3). transpupillary thermotherapy. 4). submacular surgery. 5). anti-vegf –pegaptanib sodium, ranibizumab, bevacizumab

Bevacizumab is a humanized monoclonal antiboby. It has been FDA approved for use in metastatic colorectal cancer. Antivegf bevacizumab is a cheaper alternative with promising results.[3] Studies are required to test its safety and efficacy of multiple injections in the long run. In our study we have evaluated safety & efficacy of intravitreal bevacizumab injection in patients of neovascular age related macular degeneration.

Current treatment options like photodynamic therapy ,pegaptanib and ranibizumab are expensive and require repeated treatments. Antivegf bevacizumab is a cheaper alternative with promising results. Studies are required to test its safety and efficacy of multiple injections in the long run.

The aim of our study was to evaluate the efficacy and safety of intravitreally administered Bevacizumab a humanized monoclonal anti –VEGF in Neovascular Age related Macular Degeneration.

METHODOLOGY

This non randomized, prospective study was carried out on 75 eyes of 75 patients attending the OPD at M & J Institute Of Ophthalmology and diagnosed as having Neovascular ARMD confirmed on FFA and SD-OCT .

Detailedinclusion and exclusion criteria were followed.

Following patients were excluded from this study –

1. Presence of NO perceptionorprojection of light.
2. Presence of any other retinal, macular or optic nerve pathology other than Neovascular ARMD likelyto affect visual outcome.
3. Presence of CNVM due to any cause other than Neovascular ARMD.
4. Uncontrolled intraocular pressureor eyes with preexisting glaucoma
5. Active inflammation in anterior segment.
6. Patients with advanced cataractous changes, complicated pseudophakia and corneal opacities making indirect ophthalmoscopy impossible.
7. Patients with advanced renal disease making fluorescein angiography impossible.
8. Patients with previoushistory of intervention in form of laser or intravitreal injections.
9. Patients with macular scarring.
10. Patients with history of cerebrovascular accidents or myocardial infarction or ECG abnormality like bundle branch blocks.

Written informed consent was taken before recruiting the patients for the study. The off-label use of the drug was explained to all patients. Baselineexamination like visual acuity, detailedanteriorsegment examination, slit lamp biomicroscopy and Fundus fluorescein angiography were done in all patients.
Routine blood investigations like RBS,Blood Urea and S.Creatinine were done before taking the patient for fluorescein angiography. Any history of adversedrug reactions was ruled out before doing angiography. Fluorescein angiography helped to confirm the diagnosis of CNVM. The membranes were classified into classic and occult depending on leakage pattern. They were classified into subfoveal, juxtafoveal and extrafoveal according to site of leakage. Sd-oct was done in all patients at baseline and on each visit. The same machine was used to make comparison easier. The following parameters were noted on OCT- central macular thickness, presence of subretinal, intraretinal or sub-RPE fluid, pigment epithelial detachment and other lesion components like blood, pigment and fibrosis.

After taking written informed consent all patients were injected with intravitreal Bevacizumab 1.25 mg/0.05 ml. The intravitreal injection was performed undertopical anesthesia with proparacaine eye drops. A lid speculum was used to keep the eyelashes awayfrom the conjunctiva. Povidone iodine 5% eye drops and antibiotic eye drops were instilled in the conjunctiva every five minutes for three times. The injection of Bevacizumab 1.25mg/0.05 ml was performed through a 26-gauge needle in the inferotemporal pars plana 4 mm posterior to the limbus.in phakic eyes and 3.5 mm posterior in pseudophakic eyes. After the injection, indirect ophthalmoscopy fundus examination was used to evaluate the perfusion of the central retinal artery.

Follow up visits were scheduled one week, one month postprocedure and every monthly thereafter.Visual acuity testing, iop monitoring, cataractassessment, slitlamp biomicroscopy , OCT were done at each visit. Fluorescein angiography was done as and when required.The main outcome measures were visual acuity and decrease in central macular thickness. The complications on follow up were also noted. Retreatment assessment was done every month and patients were treated as required. Retreatment was done if there was loss of more than one lines on Snellens visual acuity chart or there was any of the following on OCT- Increased retinal thickness without sub-retinal and/or intra-retinal fluid of more than 100µm, sub-retinal and/or intraretinal fluid, pigment epithelium detachment.

RESULTS

75 eyes of 75 patients were included in this non randomized prospective study. Out of 75 patient 42(56%) patients were male & 33(44%) patients were female. Patients have age range from 51 years to more than 70 years in this study.

All 75 patients underwent OCT & FFA. All patients undergone intravitreal bevacizumab injection 1.25mg/0.05 ml under all aseptic & antiseptic precautions. At the end of 1 year 8% patients required 4 or more injections, 62.66% required 3 injections & 29.33% patients required 2 injections.

Table 1: Characteristics of patients

Variable	No (%)
Visual acuity	
6/18 to 6/60	23 (30.66)
6/60 to 3/60	36 (48.00)
3/60 to HM	16 (21.33)
Type of membrane on FFA	
Classic	41 (54.66)
Occult	34 (45.33)
Central foveal thickness on OCT	
250-350 microns	17 (22.66)
350-450 microns	36 (48.00)
>450 microns	22 (29.33)
OCT characterisitics	
Cystoid edema	38
PED	43
Hemorrhage	50
Serous fluid	71

Table 2: Gain in visual and reduction in central foveal thickness acuity at the end of 1 year

Variable	No (%)
Gain in visual acuity at the end of 1 year	
>3 lines gain	16 (21.33)
2 to 3 lines gain	48 (64.00)
0 to 1 line gain	5 (6.66)
Loss of 1 line	4 (5.33)
2 to 3 lines loss	2 (2.66)
Reduction in central foveal thickness at the end of 1 yr	
>200 microns	39 (52.00)
100- 200microns	21 (28.00)
<100 microns	15 (20.00)

Table 3: Adverse reactions in patients

Adverse reactions	No.
Subconjunctival hemorrhage	30
Raised IOP	13
Conjunctivitis	14
Endophthalmitis	0
Retinal detachment	0
Lens injury	0

Any patient does not develop serious adverse effects such as endophthalmitis, retinal detachment & lens injury. Systemic side effects were not noted in any patients attributed to bevacizumab.

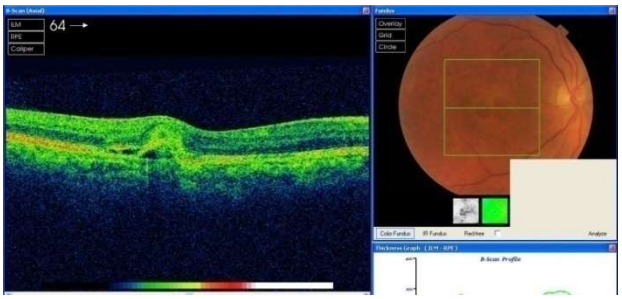

Figure 1: Pre injection OCT

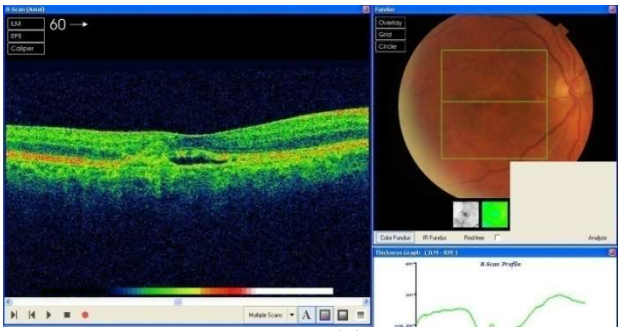

Figure 2: Post injection OCT

DISCUSSION

Age related macular degeneration (ARMD)is the major cause of severe visual loss in older adults. The prevalence in India varies from 2.7 %(dry) to 0.6 % (neovascular) in south India to 4.7 % in north India. Most ARMD patients have the dry form of the disease consisting of macular drusen or RPE abnormalities or both. Approximately 10 % of ARMD patients manifest the neovascular form of the disease. This form of the disease is accompanied by rapid loss of vision over a period of 6 to 12 months and the formation of central disciform fibrotic scar.[4]

Vision loss in the Neovascular ARMD is mainly due to two mechanisms-1) Proliferation of new capillaries is accompanied by secondary fibrosis and disorganization of the pigment epithelium and outer retina. 2)Secondary alterations in both retinal capillary and pigment epithelial permeability lead to accumulation of serous, serosanguineous fluid beneath the pigment epithelium,neurosensory retina or within the retina itself and are asscociated with acute visual dysfunction. It has now been established that vascular endothelial growth factor(VEGF) plays a principle role in the development of Neovascularization in Neovascular ARMD through its characteristics of 1) induction of angiogenesis through endothelial proliferation , migration and new capillary formation and 2) enhancement of vascular permeability.

Bevacizumab is a mouse-derived monoclonal antibody to VEGF produced by humanization of the mouse epitopes that was designed to neutralize the effects of all isoforms of VEGF in clinical disease . Preclinical studies in animal models of various tumor

cell lines as well as different forms of ocular neovascularization indicated that the fully sized antibody had excellent efficacy against the primary permeability and proliferative effects of VEGF isoforms.[5]

Ranibizumab is a humanized, murine antigen-binding fragment (Fab) with only a single affinity-matured binding site for VEGF. Ranibizumab received United States Food and Drug Administration (USFDA) approval for the treatment of neovascular AMD on June 30, 2006.

The CATT [6] (The Comparison of Age-related macular degeneration Treatment Trials) study and the IVAN[7] (The alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation randomized trial) study confirmed that both drugs might be regarded as parallel concerning visual acuity gain and safety issues.

A study by Biswas et al[8] was prospective randomized trial conducted across two centers in Kolkata, India, with 104 subjects and a total of about 302 injections in the ranibizumab group and about 216 injections in the bevacizumab group, studied results over 18 months. Parameters studied included both change in BCVA and CMT and the adverse effects of the two drugs over 18 months. They found no statistically significant difference in the efficacy and safety of ranibizumab and bevacizumab when used as intravitreal injections for treatment of CNVM due to wet AMD.

Avery RL et al[9] have shown that Bevacizumab is well tolerated and associated with improvement in vision, decreased thickness on oct and reduction in angiographic leakage. The study conducted by Avery showed that at 1, 4, 8 and 12 weeks the mean retinal thickness of central 1 mm was decreased by 61,92,89 and 67 μm, respectively ($P<0.0001$ for 1, 4 and 8 weeks and $P<0.01$ for 12 weeks).

Our study showed that 80% patients had decrease in central foveal thickness more than 100 microns from baseline at the end of one year. 85% patients had gain of 2 or more lines on Snellen's visual acuity chart from baseline.No patient had any serious local or systemic adverse reactions.

Limitations of our study is small number of patients,ICG not done,not compared with other anti-vegf drugs.

CONCLUSION

Intravitreal Bevacizumab is a safe and effective drug in treatment of neovascular age related macular degeneration in terms of improvement in best corrected visual acuity and reduction in central foveal thickness on OCT without any serious systemic or local adverse effects.

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ORIGINAL ARTICLE

ROLE OF FIBER-OPTIC BRONCHOSCOPY IN SPUTUM SMEAR NEGATIVE PULMONARY TUBERCULOSIS

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ABSTRACT

Objective: To evaluate the utility of fiberoptic bronchoscopy in sputum smear negative PTB patients.

Material and Methods: A total of 66 adult patients with sputum smear negative for Acid Fast Bacilli (AFB) and chest X-ray suggestive of pulmonary tuberculosis underwent fiberopticbronchoscopy (FOB). A thorough examination of bronchial tree was carried out and bronchoalveolarlavage (BAL) was taken and was sent for Ziehl-Neelsen staining, MGIT960 TBculture, pyogenicand fungal culture. Bronchial brushing, endo-bronchial and transbronchial lung biopsy(TBLB) wherever indicated were performed and Ziehl-Neelsen staining was performed and post bronchoscopy sputum(PBS) was also sent for Ziehl-Neelsen stain.Results are summarized in tables and percentages. Quantitative data is summarized using means& standard deviation. Cross tabulation with outcome variable of interest was done using statistical software Epi-info version 7 (7.1.1.0). A p-value of less than 0.05 was considered statistically significant.

Results: Males constituted majority of our study population. The most common age group involved in the study was 18-28 years (36.3%). cough was the most common symptom reported by 62 patients (93.93%). The past history of PTB was present 6 patients (9.09%).Majority of study population, 39 patients (59.09%) had unilateral lesion on CXR. Out of 66 clinically suspected SSN-PTB patients, 52 patients (78.7%) were finally diagnosed as having active PTB. The diagnosis other than PTB was established in 6 (9.09%) cases, which included 3 cases of fungal (Candida) pneumonia and 3 cases of bacterial (pseudomonas species, citrobacter species, serratiamarsecens) pneumonia.

Conclusions: FOB and various bronchoscopy guided procedures can provide a rapid and definitive diagnosis of PTB in sputum negative patients.

Keywords: Sputum smear negative pulmonary tuberculosis, Fiberoptic bronchoscopy, MGIT960.

INTRODUCTION

Mycobacterium tuberculosis (MTB), discovered by Robert Koch in 1882 is the leading killer of human being.[1] In 2012, WHO estimated 8.6 million incident cases of TB globally equivalent to 122 cases per 100000 population. Out of 8.6 million cases, an estimated 0.5 million were children and 2.9 million occurred among women and 1.0 to 1.2 million among people living with human immunodeficiency virus (HIV).[2] Detecting patients with active pulmonary tuberculosis (PTB) disease is an important component of tuberculosis (TB) control as early appropriate treatment renders these patients non-infectious and interrupts the chain of transmission of TB. Under the programme conditions, such as those endorsed by the World Health Organization (WHO)[3] and implemented successfully in high burden countries including India's Revised National Tuberculosis Control Programme (RNTCP)of Government of India, the diagnosis of PTB is based on sputum smear examination.[4]

However, in patients with a compatible clinical picture, sputum smears do not reveal acid-fast bacilli (AFB) in all patients. Sputum smear negative pulmonary tuberculosis (SSN-PTB) is a common clinical problem faced by the clinicians as approximately 50% of PTB cases are sputum smear negative for AFB.[5]This is particularly true in the case of children who are unable to produce an adequate sample of sputum, patients with immunosuppressed states.

Currently diagnostic criteria for SSN-PTB include at least two sputum smear negative for AFB, radiographic abnormalities consistent with active PTB, no response to a course of broad spectrum antibiotics (except in a patient for whom there is a laboratory confirmation or strong clinical evidence of HIV infection), and a decision by a clinician to treat with full course of anti TB chemotherapy.[6] A patient with

positive culture but negative AFB sputum examination is also a smear negative case of pulmonary TB. Although microscopic examination is rapid, simple and economical, it is relatively insensitive, requiring more than 10, 000 bacilli per milliliter to detect AFB. Other factors like poor quality of the sputum sample, deficiency in preparation, staining, or examination of the sputum smear can contribute to the negative results.[7] On other hand, if not treated, 64% of sputum negative suspects could need chemotherapy within 12 months.[8] Sputum culture can increase the diagnostic yield by 20-40%, although the time needed for obtaining the final result is 2-8 weeks when solid media are used or 10-40 days when automated non-radiometric systems are used.[9]ChestX-ray is also an important and widely used method for diagnosing PTB. However, it has several limitations. Chest X-ray is often unable to determine disease activity, differentiating active disease from sequelae is often difficult, and many non-tubercular diseases, such as neoplasia, pulmonary mycosis, and sarcoidosis may mimic TB radiologically.

Difficulty in diagnosis arises when a patient clinically and radiologically suspected of having active TB, but does not produce sputum. Henceforth, more aggressive procedures need to be undertaken in these patients in order to establish the diagnosis. A number of studies confirm the usefulness of fiberoptic bronchoscopy (FOB) in the diagnosis of PTB.[10-11]The main advantage of FOB is its ability to visualize the bronchial tree and collect samples directly from the site of pathology. FOB with bronchial aspiration and broncho alveolar lavage (BAL) under local anesthesia is a relatively safe procedure and well tolerated by most of the patients.[12-15] Complications are known but rare in occurrence.[16-17]

Early diagnosis of PTB prevents progression of disease, reduces morbidity and spread of disease. It also prevents permanent lung damage by fibrosis. The present study was undertaken to evaluate the role of FOB in SSN-PTB or in patients unable to produce sputum by direct visualization of bronchial tree and collecting specimens by bronchoalveolar lavage, endobronchial biopsy, transbronchial lung biopsy (TBLB) and post-bronchoscopy sputum (PBS).

METHODOLOGY

This Institutional based Prospective Study was conducted in the department of Pulmonary Medicine and Microbiology, IGMC, Shimla from July 2014 to June 2015. All consecutive patients with sputum smear negative pulmonary tuberculosis who attended the pulmonary medicine outpatient as well as inpatients were selected for the study.

Inclusion Criteria: All patients whose two sputum examination is negative for acid fast bacilli or who are unable to produce sputum and has given consent for the study.

Exclusion Criteria: Patients with Smear positive pulmonary tuberculosis, Not willing for informed consent,Pleural effusion,Pregnancy,Accessible lymph node,Contraindication to FOB,Seriously ill patients were excluded.

Procedure: Patients presenting with respiratory symptoms such as cough for at least 2 weeks duration, fever, hemoptysis, anorexia and loss of weight, and two sputum smears negative forAFB or unable to produce sputum and radiographic appearances suggestive of PTB were evaluated. Physical examination, routine investigations, and assessment of patients for the fitness of bronchoscopy procedure were done. Lignocaine sensitivity and premedication with injection atropine 0.6 mg intramuscularly were given to all patients one hour before the procedure. FOB was performed using PENTAX video bronchoscope EB-1970k with xenon light source through transnasal or oral route and all patients received lignocaine 2% topically that is necessary to minimize coughing. During bronchoscopy, patient's vital parameters such as blood pressure, heart rate, respiratory rate and oxygen saturation were monitored.All procedures were carried out as per the International recommendations.[18-19] A thorough examination of bronchial tree was carried out and bronchoalveolar lavage (BAL) was taken. Bronchial brushing, endobronchial and transbronchial lung biopsy (TBLB) wherever indicated were performed and post bronchoscopy sputum (PBS) was also sent for Ziehl-Neelsen stain. The Ziehl-Neelsen staining was performed in BAL, BB, endo-bronchial and TBLB samples also. Smears were examined under oil immersion lens. BAL sample was also sent for MGIT960 TB culture,pyogenic and fungal culture.

The data collected was entered into a computer in MS Excel spreadsheet 2007. Results are summarized in tables and percentages. Quantitative data issummarized using means& standard deviation. This was done by using MS Excel 2007. Cross tabulation with outcome variable of interest wasdone using statistical software Epi-info version 7 (7.1.1.0). A p-value of less than 0.05 was considered statistically significant. Sensitivity, specificity, positive predictive value, negative predictive value of the testswere calculated using standard statistical formulas.

RESULTS

The total Number of patients involved in the study were 66, out of which 46 (69.69%) were male and 20 (30.30%) were female. Mean age of study population was 41.18 years.Mean age among male and female were 42.35 and 38.50 years respectively.

Table 1: Result of FOB in diagnosed PTB cases

FOB Specimen	No. (%)
BAL smear for ZNS	15 (22.72)
BAL for MGIT960 TB culture	48 (72.72)
BAL for fungal culture	4 (6.06)
BAL for pyogenic culture	2 (3.03)
Bronchial brushing for ZNS	1 (1.51)
Bronchial brush for cytology	0 (0)
TBLB/Endobronchial biopsy for ZNS	0 (0)
TBLB/Endobronchial biopsy for HPE	4 (6.06)
Post bronchoscopic sputum	4 (6.06)

ZNS=Ziehl-Neelsen staining

Among 66 patients cough was the most common symptom being reported by 62 patients (93.93%), followed by dyspnea in 57 patients (86.36%), chest pain in 33 patients (50%), fever in 30 patients (45.45%), and hemoptysis in 19 patients (28.78%). Past history of PTB in 6 patients (9.09%), diabetes mellitus in 3 patients (4.54%), and hypertension in one patient (1.51%). Among patients with PTB, 19 were smoker and 33 were non-smoker, 13 patients were alcoholic and 39 were non-alcoholics. Four (6.06%) patients had family history of PTB. Chest x-ray was performed in all patients .Among patients with active PTB, 23 had right sided lesion and 8 had left sided lesion. Bilateral lesion was seen in 21 patients. 50 patients (75.76%) had infiltrates and 16 patients (24.24%) had cavitatory lesions. Based on radiological classification of disease extent by National Tuberculosis Association of USA, the lesions on CXR were classified into minimal, moderately advanced and far advanced. In our study, 31 patients (46.96%) had mild lesions, 28 patients (42.42%) had moderately advanced lesions and 7 patients (10.60%) had far advanced lesions.

Out of 66 patients, 57 were subjected to CT chest for elucidating the underlying cause and for localization, 1 patients (17.54%) were finally diagnosed as non-PTB cases and 47 patients (82.45%) were finally diagnosed as PTB. The most common radiological lesions on CT chest was consolidation seen in 30 patients (45.45%), followed by nodular opacities in 26 patients (39.39%), cavitation in 17 patients (25.75%), tree in bud appearance in 17 patients (25.75%) and consolidation with associated loss of volume in 4 patients (6.06%).The most common FOB finding was normal bronchial tree which was observed in 44 patients (66.66%). Other findings include secretions in 6 patients (9.09%), erythema and ulceration in 7 patients (10.60%), bronchial stenosis in 6 patients (9.09%), distortion in 3 patients (4.54%) and growth in one patient (1.51%).

Table 2: Sensitivity, specificity, PPV and NPV of smear in FOB specimens

FOB Specimen	BAL MGIT TB culture positive	BAL MGIT TB culture negative	Sensitivity (%)	Specificity (%)	False –ve (%)	False +ve (%)	PPV (%)	NPV (%)
Z N Staining								
Smear Positive	11	4	22.9	77.7	77.0	22.2	73.3	27.4
Smear Negative	37	14						
Post Bronchoscopy sputum								
Smear Positive	4	0	8.3	100	91.6	0	100	29
Smear Negative	44	18						

Among the 66 patients included in the study, BAL was done in all the patients and subjected to Ziehl-Neelsen staining and MGIT960 TB culture. A positive microscopic yield was obtained in 15 (22.72%) patients, MGIT960 culture was positive in 48(72.72%) patients. Bronchial brushings was taken in 3 cases, only one bronchial brushing yielded positive result by Ziehl-Neelsen staining smear.Endobronchial biopsy was done in three cases and TBLB was done in one case. Histopathological examination revealed caseating granulomain all 4 cases. A positive post bronchoscopic sputum yield was found in 4 patients (6.06%) as shown in Table-1.

Among the 52 diagnosed cases of PTB, BAL was smear positive in 11cases, negative in 37 cases, the sensitivity and specificity being 22.9% and 77.7% respectively with PPV of 73.3% and NPV of 27.4% as shown in table-2. Similarly post-bronchoscopic sputum smear was positive in 4 cases, negative in 44 cases, the sensitivity and specificity being 8.3% and 100% respectively with PPV of 100% and NPV of 29%.

Table 3: Diagnostic yield of FOB

Diagnosis	No. (%)
Total PTB cases diagnosed	52 (78.78)
BAL with ZN staining	15 (22.72)
BAL with MGIT960 TB culture	48 (72.72)
Total cases of other diseases diagnosed	6 (9.09)
Fungal pneumonia	4 (6.06)
Bacterial pneumonia	2 (3.03)
Malignancy	0

The complications following bronchoscopic procedure were very few, minor hemorrhage following TBLB was seen only in one patient (1.51%).Serious complications like respiratory failure, cardiac arrhythmia, cardiac arrest and pneumothorax was not seen in our study group.

Among the 66 cases studied the total number of PTB cases diagnosed was 52 (78.78%) as shown in table-3. Total number of PTB cases having smear +ve on ZN staining was 15 (22.72%) and total number of PTB cases showed growth on MGIT 960 TB culture was 48 (72.72%). The total number of cases, of other diseases diagnosed was 6 (9.09%), which included 3 cases of fungal (Candida) pneumonia and 3 cases of bacterial (pseudomonas species, citrobacter species, serratiasmarsecens) pneumonia.

DISCUSSION

Despite the discovery of the tubercle bacilli more than a hundred years ago and all the advances made in our knowledge of the disease, TB is still a major health problem facing mankind, particularly in developing countries. India accounts for an estimated 2.2 million of the 8.6 million new cases of TB that occur each year globally and harbors more than twice as many cases as any other country.[2]

The mainstay of diagnosis of PTB is the detection of AFB in sputum samples. Sputum microscopy is a highly specific and low-cost test for the diagnosis of PTB. It is an essential component of the directly observed treatment short-course (DOTS) strategy of the WHO. However, sputum smear is not always positive. Smear negative, culture positive state has been observed in 22% to 61% of cases and contributes to the burden of SSN-PTB.[8,20,21.]

SSN-PTB, that includes patients with clinical and radiological evidence of pulmonary TB but repeatedly negative sputum smear for AFB, is a common clinical problem faced by the clinicians, particularly in countries affected by the dual TB/HIV epidemics. SSN-PTB is also infectious but the infectivity rate is less compared to patients with smear-positive PTB. Moreover, 50% of patients with SSN-PTB would need ATT by the end of 12 months if untreated.[8,22]Therefore, emphasis should be put on early diagnosis of SSN-PTB as early effective treatment renders the patients with active PTB non-infectious and interrupts the chain of transmission of TB.

The most remarkable advantage with the recent methods of automated mycobacterial culture lies in their earlier detection of culture-positivity. Among them the earliest and most widely studied method, viz. BACTEC-460 system, requires sophisticated instrumentation and the provision of safe handling and disposal of radioactive waste. Alternate methods like MGIT 960 and MB Redox tube systems are based on detection of fluorescent or colorimetric signals and, hence, are free from the hazards of radioactive handling.

In our study total 66 patients were included and all underwent bronchoscopy. The most common gross FOB finding was normal bronchial tree which was observed in 44 patients (66.66%). Other findings were secretions in 6 patients (9.09%), erythema and ulceration in 7 patients (10.60%), bronchial stenosis in 6 patients (9.09%), distortion in 3 patients (4.54%), and growth in one patient (1.51%). These findings are in accordance with the various other studies as by Rawat *et al.*[23]who reported normal bronchial tree in 48% patients, normal bronchial tree with secretions in 25%, normal bronchial tree with distortion in 9.6% patients, erythema, ulceration, nodularity in 36.5% patients. Growth was not seen in any patient. Kulpati *et al.*[24]observed that coating of mucosa of involved segments with yellowish white secretions in almost all patients and also revealed mild to moderate hyperemia after bronchial wash. Segmental bronchus was narrowed in 20% patients, and ulceration was seen in 20% patients. Similar observations were made by Panda *et al.*[25]According to their study, 44% had normal bronchial mucosa, 21% had unhealthy mucosa with granulations, 35% had discharge of mucous from bronchus, 5% had growth, 3% had external compression and three per cent had bleeding from bronchus and some cases had multiple findings. Quaiser *et al.*[26]revealed no lesion in 19 (47.5%) patients, gross lesion in 21 (52.5%) patients, of which 6 (15%) patients showed features suggestive of PTB (endobronchial inflammation with distortion and stenosis of bronchi`, tubercles), 8 (20%) patients had generalized chronic inflammation and 7 (17.5%) patients had features of acute inflammation.

BAL was done in all the patients and subjected to Ziehl-Neelsen staining and MGIT-960 TB culture.A positive microscopic yield was obtained in 15 patients (22.72%), MGIT960 culture was positive in 48 patients (72.72%). Bronchial brushings was taken in 3 cases, only one bronchial brushing yielded positive result by Ziehl-Neelsen staining smear. Endobronchial biopsy was done in three cases and TBLB was done in one case and histopathological examination revealed caseating granuloma in all 4 cases. A positive PBS yield was found in 4 patients (6.06%). In Rawat *et al.*[23] study culture by MGIT960 method yielded the growth of MTB in 51.9% patients, and AFB smear positive in 23% patients. Similarly Chawla *et al.*[27]showed that the positive yield of BAL smear for AFB was 20.33% and Yuksekol I *et al.*[28]showed BAL positive for AFB smear in 23% and 50% positive for culture whereasBaughman *et al.*[29]showed a positive yield by BAL fluid smear examination and MTB culture as 68% and 92% respectively which is

much higher than our study. Wongthim *et al*[30] reported BB having the highest diagnostic yield being positive in 33 of the 65 (51%; 4.6% exclusively positive) patients. In our study the low yield of bronchial brushings may be due to the fact that it was done in very few cases because majority of patients had normal bronchial anatomy. Other similar studies in the literature such as Bachh*etal.*[31]whoreported the PBS smear yield as 18.33% while Sarkar *et al.*[32] have reported a very high (73%) positive yields of PBS. In our study immediate diagnosis was possible in 28.78% cases of PTB by demonstrating positive AFB in FOB guided specimens and histopathological evidence of caseating granuloma. Sarkar et al[32]reported immediate diagnosis in 73% of cases. The yield of immediate diagnosis of active PTB in SSN-PTB suspects varies widely from 9% to 73% in the similar studies reported in the literature.[33,34,35.] The overall diagnostic yield of smear examination, MGIT 960 culture and demonstration of granuloma from various bronchoscopic specimens was found to be 78.7% (52 cases) in our study. The overall yield of FOB in the diagnosis of active PTB among SSN-PTB suspects varies widely in the literature ranging from 35.7% to 95%.[24,27,30-33,36-41.] Shin *et al.*[42]reported sensitivity, specificity, PPV and NPV of BAL for mycobacterial culture in his study as 75.9%, 97.2%, 95.3% and 84.3%respectively.Result of this study showed higher value than our study. Therefore, FOB is a useful procedure in the diagnosis of PTB.

Furthermore, Jacomelli*et al.*[43]reportedthat for the diagnosis of tuberculosis, BAL showed a sensitivity and a specificity of 60% and 100% respectively. The sensitivity and specificity in this study group was higher than our study.Therefore bronchoscopy is a safe and effective method for the diagnosis of PTB in patients in whom diagnosis by sputum smear microscopy is not possible. In the present study, FOB was useful not only for the diagnosis of tuberculosis but also for the identification of other pathologies, especially pulmonary infection. Other pathologies were diagnosed in 6 (9.09%) patients. Three patients had fungal (Candida) pneumonia and 3 patients had bacterial (Pseudomonas, citrobacter, serratiamarsecens) pneumonia. Singhal*et al.*[41] reported 64.3% cases other than active PTB including 42.9% cases of community acquired pneumonia (CAP), 7.2% cases of neoplasm, 11.9% cases of foreign bodies, and 2.3% case of ABPA.

In our study the complications following bronchoscopic procedure were very few, minor hemorrhage following TBLB was seen only in one patient (1.51%). Serious complications like respiratory failure, cardiac arrhythmia, cardiac arrest and pneumothorax did not occur in our study group. In another study assessing complications ofFOB in 1328 children, De Blic*et al.*[44]have concluded that bronchoscopy is safe in children, recording a minor complication rate of 5.2%, in the form of desaturation, excessive cough, nausea, transient laryngospasm and epistaxis and major complications occurred in 1.7% only. Sinha *et al.*[45] found as complications hypoxia (2.4%), post-bronchoscopy bleeding (1.2%), fever (1.2%), chest pain (1.7%) and pneumothorax (0.51%). The reported literature reinforces the fact that FOB in properly selectedpatients has very minimal complication rates, which was the case in our study also.

LIMITATIONS

There are few limitations in this study. Firstly, a major fraction of the recruited patients did not have significant expectoration and it was not possible to perform both sputum and BAL culture, and also owing to the fact that automated MGIT960 liquid culture is much more superior than solid culture on Lowenstein Jensen medium. Hence we decided to include only BAL samples in our study for MGIT 960 TB culture. The number of subjects was also small in our study.

CONCLUSION

India is among the 22 high burden countries of PTB, and due to high contagious nature of PTB, its early recognition is of utmost importance. The results of present study suggest that FOB is a useful tool in diagnosing SSN-PTB patients. FOB reveals a high bacteriological confirmation of diagnosis in SSN-PTB patients. FOB is also a safe procedure. FOB also helps in ruling out non-PTB conditions like bacterial pneumonia. We, therefore, conclude that FOB and various bronchoscopy guided procedures can provide a rapid and definitive diagnosis of PTB in sputum negative patients.

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ORIGINAL ARTICLE

STUDY ON FACTORS ASSOCIATED WITH CHRONIC LOW BACK PAIN IN WESTERN INDIA

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ABSTRACT

Introduction: Low back pain is a leading cause of disability. It occurs in similar proportions in all cultures, interferes with quality of life and work performance, and is the most common reason for medical consultations. Few cases of back pain are due to specific causes; most cases are non-specific. Acute back pain is the most common presentation and is usually self-limiting, lasting less than three months regardless of treatment. Chronic back pain is a more difficult problem, which often has strong psychological overlay: work dissatisfaction, boredom, and a generous compensation system contribute to it.

Methodology: This is a retrospective study. The study was conducted in private multispecialty hospital of Ahmedabad, Gujarat. Data from April 2014 to March 2015 was analyzed. Permission was taken from the hospital authority to conduct the study and stringent confidentiality of data was maintained at all levels of the project.

Result: We have analyzed data of 210 patients diagnosed with chronic low back pain. People between age of 36 years to 40 years were most common culprits. Among these, 82 (39.05%) were male and 128 (60.95%) were female. Among males, 65 (79.27) were overweight (BMI >= 25.00) and among females, 95 (74.22%) were overweight. Disc prolapse was most common diagnosis in both males and females. It was followed by fractures and Lumber spondylosis.

Conclusion: Females were more affected by Lower back pain. People in age group of 36 years to 40 years were commonly affected. Disc prolapsed was most common the most common diagnosis.

Keywords: Lower Back Pain, Lumbar spondylosis, Disc prolapse

INTRODUCTION

Low back pain is a leading cause of disability. It occurs in similar proportions in all cultures, interferes with quality of life and work performance, and is the most common reason for medical consultations. Low back pain (LAP) is an extremely common health problem and a leading cause of disability.[1-4] It occurs in similar proportions in all cultures, interferes with quality of life and work performance, and is the most common reason for medical consultations. Low back pain is the leading cause of activity limitation and work absence throughout much of the world, and it causes a great economic burden on individuals, communities and governments.[5]

The point prevalence of LBP is 28.5% found in an Asian country.[6] The lifetime prevalence of low back pain is reported to be over 70%. But globally, the annual prevalence of LBP has been estimated at 38%. In general, LBP resolves within weeks, but may recur in 24-50% of cases within 1 year. Thus, the identification of risk factors for LBP is important in the prevention of recurrent and possibly chronic LBP.[7] The prevalence of LBP in children is low (1%-6%) but increases rapidly (18%- 50%) in the adolescent population.[8,9]

The prevalence of LBP peaks around the end of the sixth decade of life. Few cases of back pain are due to specific causes; most cases are non-specific. Acute back pain is the most common presentation and is usually self-limiting, lasting less than three months regardless of treatment. Chronic back pain is a more difficult problem, which often has strong psychological overlay: work dissatisfaction, boredom, and a generous compensation system contribute to it. It is generally assumed that overweight and low back pain are related.[10] However, scientific evidence to support this relationship is not fully conclusive.[11,12]. Some studies have reported that subjects who carry excessive abdominal fat mass over a long period may be at

risk of low back pain, as a result of altered posture to counter balance the protruding fat mass.[13]

The present study, is aimed at finding the factors associated with Chronic Low back pain.

METHODOLOGY

The present study was a retrospective study. The study was conducted in a private multispecialty hospital of Ahmedabad, Gujarat. All patients attending orthopedic OPD forms study population.

Data of all patients having history of back pain for last six months or more and not relieved by primary treatment of pain killers and muscle relaxant during April 2014 to March 2015 were analyzed. Permission was taken from the hospital authority to conduct the study and stringent confidentiality of data was maintained at all levels of the project.

Completeness of data were assessed. Basic information like name, age, gender, duration of pain, height, weight, diagnosis etc. details were taken. Patients not having this data were excluded from the records.

Data were entered and analysed by MS excel. Frequency and percentage were calculated for all variables.

Total 236 patients were eligible to be included in the study. Out of these, 26 patients were not having complete information. Data of these 26 patients were excluded from the master dataset. Thus, data of total 210 patients were included and analysed for the study.

RESULTS

There were total 210 patients included in the study.

Table 1 shows age and gender wise distribution of patients having chronic low back pain. There were total 82 (39.05%) males and 128 (60.95%) females among total 210 patients. Age wise distribution of patients shows that maximum number of patients 65(30.95%) were from age group of 36 to 40 years. Among males and females maximum patients were also from age group of 36 to 40 years. (25.61%).

Table 2 shows BMI and gender wise distribution of patients. There were total 160 (76.19%) patients having BMI of >= 25.00. Gender wise distribution of patients also showed that maximum number of patients were having BMI >= 25.00.

Table 3 shows gender wise different diagnosis of patients. It was observed that maximum numbers of patients were having Disc Prolapse. It was followed by Fractures, Lumber Spondylosis and Spondylolisthesis. Same trend was seen in both male and female.

Table 1: Age group and gender wise distribution of patients

Age (In years)	Male (%)	Female (%)	Total (%)
<=30	8 (9.76)	5 (3.91)	13 (6.19)
31-35	11 (13.41)	19 (14.84)	30 (14.29)
36-40	21 (25.61)	44 (34.38)	65 (30.95)
41-45	14 (17.07)	22 (17.19)	36 (17.14)
46-50	12 (14.63)	12 (9.38)	24 (11.43)
51-55	6 (7.32)	11 (8.59)	17 (8.10)
56-60	7 (8.54)	9 (7.03)	16 (7.62)
>60	3 (3.66)	6 (4.69)	9 (4.29)
Total	**82 (100)**	**128 (100)**	**210 (100)**

Table 2: BMI and gender wise distribution of patients

BMI	Male (%)	Female (%)	Total (%)
<18.50 (Underweight)	6 (7.32)	11 (8.59)	17 (8.10)
18.50-24.99 (Normal)	11 (13.41)	22 (17.19)	33 (15.71)
>=25.00 (Overweight)	65 (79.27)	95 (74.22)	160(76.19)
Total	**82 (100)**	**128 (100)**	**210 (100)**

Table 3: Different Diagnosis of Patients

Diagnosis	Male (%)	Female (%)	Total
Lumbar spondylosis	9 (10.98)	19 (14.84)	28
Disc prolapse	29 (35.37)	42 (32.81)	71
Spondylolisthesis	9 (10.98)	18 (14.06)	27
Lumbar spinal stenosis	8 (9.76)	11 (8.59)	19
Fractures	14 (17.07)	23 (17.97)	37
Tuberculosis (Koch's) spine	7 (8.54)	9 (7.03)	16
Nonspecific	6 (7.32)	6 (4.69)	12

DISCUSSION

In present study records of total 210 patients affected with chronic back pain was analysed. Our study shows that Lower back pain was more common among women than men. Age wise distribution of patients shows that maximum number of patients were from age group of 36 to 40 years.

Many studies reported the association between age and LBP among Asian population [14] as well as the western population.[15,16]Some studies reported that age ≥35 years was found to have 9 times more risk as compared to <35 years.[17,18] In another study found that LBP at age 18 significantly increased the risk of LBP at age 30.[19] It showed a prevalence of 30.8% in the age group (20-30years). Thus, many studies reports the occurrence of back pain at earlier stage of life. The association between gender and LBP had been reported by previous studies. Many studies shows female preponderance in lower back pain.[20]

Our study shows that 76.19% patients of lower back pain were having BMI of >= 25.00. This was correct for both gender. There are several studies that conform to the pattern that height is not correlated with the occurrence of low back pain in women, though

in men many studies reported a positive correlation.[21,22] This is in consistent with many studies. Overweight and increased waist-hip ratio serves both the predictor and risk factor for Lower back pain.[23,24,25]

Increased lordosis in obese persons in order to maintain the centre of gravity due to excess weight may be responsible for the complaint of low back pain.[21] Persons with a high percent body fat had high levels of disability. Some studies showed that association between obesity and LBP has been reported to be stronger among women than among men [23,24]

It was observed in our study that maximum number of patients were having Disc Prolapse. It was followed by Fractures, Lumber Spondylosis and Spondylolisthesis. Same trend was seen in both male and female.

CONCLUSIONS

By this study we conclude that females were more affected by Lower back pain. People in age group of 36 years to 40 years were commonly affected. Disc prolapsed was most common the most common diagnosis.

LIMITATIONS

As it was a record based retrospective study in private hospital, we could not study more factors as records of many patients were not maintained properly. A prospective study is needed to address the issue.

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ORIGINAL ARTICLE

RETROSPECTIVE STUDY OF HORMONE RECEPTOR STATUS IN BREAST CANCER PATIENTS IN CENTRAL INDIA

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ABSTRACT

Background: Breast cancer, in India, is the second most cancer in females. Hormone receptor status with ER/PR is now routinely done in patients with invasive carcinoma. We have done single institutional retrospective study with the aim to evaluate the ER, PR receptors in invasive breast carcinomas patients in central India.

Methodology: This retrospective study was done on breast carcinoma patients coming to Sri Aurobindo institute of medical sciences, Indore. Data were collective from medical records of breast carcinoma patients from January 2013 to may 2016.Total 149 cases of histopathologically diagnosed carcinoma breast were registered out of which 144 patients with different histology's were evaluated taking into account various parameters like age, sex ,histology, stage, background ,menstrual status, hormone receptor status.

Results: Out of 149 patients registered 144 patient's data were available for hormone receptors status. The age range was 25-85 years with a median of 53 years. Out of 144 patients, 78 percent were of invasive ductal carcinoma and 16 percent were of invasive lobular carcinoma. Our data showed total 39 percent patients were positive with both ER and PR(ER+PR+) and 44% patients were negative for both ER and PR(ER-PR-). Overall ER+ was 54% and PR+ was 44%. Out of total 80 hormone positive patients 28 % were only ER positive and 2.5% were only PR positive.

Conclusion: Hormone receptor positive status is low compared to western population and comparable with other Indian population studies.

Keyword- Hormone receptors, Breast cancer

INTRODUCTION

Breast cancer is the second most common cancer among women in India after carcinoma cervix.Where as in western countries breast cancer is the most common malignancy.[1] Breast carcinoma remains as a leading cause of death worldwide.The most important determinant in the treatment and outcome is early and accurate diagnosis.

Beaton's showed the role of estrogen in breast cancer by showing regression of breast cancer following oophorectomy over 100 year's ago.[2]Estrogen has a role of regulation of epithelial cells differentiation and proliferation. Estrogen works by interacting with estrogen receptor (ER) in the nucleus. Estrogen and progesterone has an important role in the promotion and progression of hormone receptor-positive breast cancer so endocrine therapy is the primary component in the treatment of hormone-sensitive breast cancer in the adjuvant and metastatic settings. Exposure of estrogen for prolonged period is an important risk factor for breast cancer. Progesterone receptor (PR) expression in normal breast epithelium is regulated by ER.[3]Hormone receptor status is considered to be important prognostic factors.[4] ER and PR status is routinely done nowadays to determine the need of hormonal therapy. We have done single institutional retrospective study with the aim to evaluate the ER, PR receptors in invasive breast carcinomas patients in central India.

METHODOLOGY

Breast cancer patients coming to Sri Aurobindo institute of medical sciences, Indore, from January 2013 to may 2016, were included in this retrospective study after approval from ethics committee of the institute. The histopathology reports and hormonal receptors status were accessed from medical records. We have taken into account the age, histology, stage, menstrual status, hormone receptors. There were to-

tal 149 cases of invasive breast carcinomas were registered. These 149 cases of breast carcinoma patients underwent primary surgery at the center during this period. In the present study, 144 cases of breast carcinoma with different histology were evaluated prior to any Radiotherapy, chemotherapy and hormone therapy. Breast carcinoma cases with unknown hormone receptor status were excluded. Patients with incomplete information were also excluded. Immunostaining was done on thin sections of formalin-fixed, paraffin-embedded tissue, or on sectioned frozen specimens. Initially, 4 to 5 micron sections were cut and mounted on protein-coated glass slides. Sections were heated to uncover hidden protein epitopes and exposed to a primary anti-ER and/or anti-PR antibody. A secondary antibody that recognizes the first, which is attached to an enzyme such as horseradish peroxidase, was then added. This linked enzyme converts substrates like diaminobenzidine into colored molecules upon exposure to a developer. Tissue sections were then counterstained, and the amount of ER or PR protein present was semi-quantitated according to the presence of nuclear staining. If 10% of tumor nuclei stained positive were interpreted as positive for hormone receptor. A semi-quantitative method based on intensity of nuclear staining and distribution of positive nuclei was used for Scoring. A scoring scale was used scoring 1–3 for each of these two components. Weak, moderate and strong staining was shown by 1, 2, 3 respectively. Score 1 referred to < 33%, 2 for 33–66% and 3 for > 66% of positive nuclei for the percentage of stained cells.

RESULTS

The age range (Table.1) was wide (25-85 years) with a median age of 53 years. Out of 144 cases included in our study 142 (98.61%) were females and only 2(1.4%) was male. Maximum numbers of patients were over 50 years. Infiltrating duct cell carcinoma (NOS) was the most common type (78%) followed by infiltrating lobular carcinoma (16%). Other variants were 6% including colloidal, papillary, mucinous carcinoma. Out of total patient population urban population was 68% compared to 32% of rural population. Total 56 % patients were hormone receptor positive either ER or PR. Postmenopausal patients were 57% whereas premenopausal patients were 43%.

Out of 144 patients, 18 % were metastatic, 40% locally advanced and 42% patients were early stage. In our analysis ,hormone receptor status was stratified to assess separately the rates of ER+,ER–,PR-positive (PR+),PR–, ER+/PR+, ER+/PR–, ER–/PR+, and ER–/PR– tumors.

Table 1: Clinical, histological, pathological characteristics of cases

Characteristics	Cases (%)
Age	
<30	7(5.0)
30-50	65(45.0)
>50	72(50.0)
Sex	
Female	142(98.6)
Male	2(1.4)
Hormone receptor	
Positive	80(56.0)
Negative	64(44.0)
Histology	
Invasive ductal carcinoma	112(78.0)
Invasive lobular carcinoma	23(16.0)
Others	9(6.0)
Disease stage	
Early stage	57(40.0)
Locally advanced	60(42.0)
Metastatic	26(18.0)
Background	
Urban	98(68.0)
Rural	46(32.0)
Menstrual status	
Premenopausal	61 (43.0)
Postmenopausal	81(57.0)

Table 2: Hormone receptor status

Hormone receptor status	No. (%)
ER+PR+	56(39.0)
ER+PR-	22(28.0)
ER-PR+	2(2.5)
ER-PR-	64(44.0)
ER+	78(54.0)
PR+	57(40.0)
Strong staining	60(75.0)
Weak staining	20(25.0)

Our data showed (Table.2) total 39% patients were with both ER and PR (ER+/PR+) and 44% were negative for ER&PR(ER–/PR–) receptors. Overall ER positive were 54% and PR positive were 44%. Out of total 80 hormone positive patients 28 % were only ER positive and 2.5% were only PR positive. Strong staining was present in 75% patients compare to 25% weak staining.

DISCUSSION

American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) recommend that both estrogen receptor (ER) and progesterone receptor (PR) analysis should be performed routinely in all invasive breast cancers, and the information be used to select patients for endocrine therapy since there is evidence of potential benefit of PR testing to predict response of ER-negative, PR-positive patients[5-7], usually because such tumors may be falsely ER negative.

The responsiveness of a tumor to endocrine therapy is an important parameter in breast cancer management. However, not all patients with breast cancer benefit from endocrine therapy. Tumor showing ER and/or PR can best identify those women who are most likely to benefit from endocrine therapy. Tumors that are negative for ER and PR are unlikely to respond to endocrine therapy and are better served by cytotoxic chemotherapy. Largely due to their predictive value, measurement of these receptors has become a routine part of the evaluation of breast cancers. Our study analyzed 144 patients of breast cancer from central Indian state Madhya Pradesh. The estrogen and progesterone status, clinical characteristics histological subtype, and immunohistochemical staining for receptors were studied. Infiltrating duct carcinoma was found in 78% of patients and was the major histological type of breast cancer, remaining 16 % with lobular carcinoma.

On immunohistochemical (IHC)staining estrogen receptor positivity was found in 54% and progesterone receptor positivity in 44%.The frequency of combined positive estrogen(ER+PR+) and progesterone receptor cases were 39 % and combined negative estrogen and progesterone (ER-PR-)receptor cases were 44%. Overall ER+ were 54% and PR+ were 44%.Overall ER and PR positivity rate is lower in our study then western studies but consistent with other studies done on Indian patients.[8] In two studies done from India by Desai et al and Vaidyanathan et al showed ER to be 32% and 50 % respectively.[9-10] Out of total 80 hormone positive patients 28 % were only ER positive and 2.5% were only PR positive in our analysis.

Combined negative estrogen and progesterone receptor status with high frequency have also been reported in several Indian studies.[9]The relationships between menstrual status and hormone receptor status in our study shows higher positivity of ER and PR in postmenopausal patients compared to premenopausal patients. Our study analysis shows that hormone receptor positivity increases with age, which has been proved in many studies. A variation in steroid receptor positivity variation has also been reported in certain Asian population with the lower rates of ER and PR reactivity.[9] Overall our study shows low hormone receptor positivity compared to western countries population.Environmental, lifestyle, socio-demographic and ethnicity and genetic factors variation are the reasons behind the difference in hormonal receptor positivity among all populations.[12]

CONCLUSION

Hormone receptor positive status is low compared to western population and comparable with other Indian population studies.

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ORIGINAL ARTICLE

A STUDY ON CLINICAL PROFILE OF PATIENTS PRESENTING WITH RHEUMATOID ARTHRITIS IN A TERTIARY CARE HOSPITAL OF PUNE CITY

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ABSTRACT

Background: The clinical picture of Rheumatoid arthritis is mainly related to the affection of peripheral joints. The present study was planned with an objective to study clinical and laboratory profile of patients presenting with rheumatoid arthritis.

Methodology: The present study was a cross-sectional study conducted on cases of rheumatoid arthritis. Special emphasis was placed on the clinical presentation grading at the time of presentation with associated etiological factors and exacerbating factors. All the patients were also subjected to necessary blood investigations and relevant radiological investigations.

Results: Among the total 100 cases of RA, maximum incidence of rheumatoid arthritis was seen in the age group of 31 – 40 years (46%) and 41-50 years (30%). The commonest clinical features noted was joint pain (100%), commonest joint involved was proximal interphalangeal and metacarpophalangeal joints (96%), commonest upper limb deformity was ulnar deviation of digits (40%) and commonest radiological changes were juxta articular osteopenia and soft tissue swelling (74%). Rheumatoid arthritis factor was positive in 76 % (76 cases) and Anti CCP was positive in 94% (94 cases) of the patients.

Conclusion: It is concluded from the present study that most common predisposing factors were family history and smoking and commonest exacerbating factor was climatic changes. The most common clinical features are morning stiffness, joint pain, joint swelling and limitation of joint movement.

Keywords: Rheumatoid arthritis, clinical profile, laboratory profile, joint involvement

INTRODUCTION

Rheumatoid arthritis is one of the commonest connective tissue disorder in the world.[1] Worldwide, the prevalence of rheumatoid arthritis is 0.8% of the total population. In India, the prevalence of the disease is estimated to be about 0.75%.[2] Rheumatoid arthritis occurs throughout the world and affects all races, but some races are less affected, such as the rural sub-Saharan Africa and Carribean blacks.[3]

The clinical picture of Rheumatoid arthritis is mainly related to the affection of peripheral joints. Symmetric involvement of hands, wrist, knee and feet are classically described. Extra-articular involvement of organs like skin, heart, lungs and eyes can also be significant. Prodromal symptoms such as fatigue, weight loss, transient pain in muscles and joints, sweating, paraesthesia and migrant swelling are often reported before the onset of the classical clinical picture.[4]

There is no single diagnostic test for the confirmation of Rheumatoid arthritis. Investigations are therefore used only to supplement the clinical findings. The most significant investigatory findings increased levels of rheumatoid factor and radiographic changes in the joints. Erythrocyte sedimentation rates, C-reactive protein levels, circulating immune complexes, and platelet counts are often elevated in Rheumatoid arthritis and serve as indicators of disease activity.[5] The present study was planned with an objective to study clinical and laboratory profile of patients presenting with rheumatoid arthritis.

METHODOLOGY

The present study was a cross-sectional study conducted on cases of rheumatoid arthritis coming to the Outdoor Patient Department (OPD) and Indoor Patient Department (IPD) of Padmashree Dr. D.Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune. The data collection of study was conducted over the period of 6 months from January 2014 to June 2014.

All the cases of rheumatoid arthritis in the outpatient and inpatient department were evaluated according to the predesigned questionnaire. Special emphasis was placed on the clinical presentation grading at the time of presentation with associated etiological factors and exacerbating factors. All the patients were also subjected to necessary blood investigations and relevant radiological investigations. The cases which are included in the study were more than 20 years of age and having joint pains, signs of inflammation, involving mono or polyarticular joints that satisfied the diagnostic criteria for rheumatoid arthritis. Those cases who had arthritis as part of an established disease, such as, TB arthritis, gonoccocal arthritis and with complaints of arthralgia that did not satisfy the diagnostic criteria were excluded from the study. Approval of the Institutional Ethical Committee was taken prior to the commencement of the study. The cases were included in the study after taking informed voluntary consent of the participants.

Diagnostic Criteria: Revised Criteria for Diagnosis, American College of Rheumatology

1. Morning stiffness - This occurs in and around the joints and lasts at least 1 hour before maximal improvement.
2. Arthritis of 3 or more joint areas - At least 3 joint areas simultaneously have soft tissue swelling or fluid (not bony overgrowth) observed by a physician. The 14 possible areas include the right and left proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle, and metatarsophalangeal (MTP) joints.
3. Arthritis of hand joints - At least one area in a wrist, MCP, or PIP joint is swollen.
4. Symmetric arthritis (simultaneous involvement of the same joint areas on both sides of the body). Bilateral involvement of PIPs, MCPS, and MTPS is acceptable without absolute symmetry.
5. Rheumatoid nodules - Subcutaneous nodules are present over bony prominences or extensor surfaces or in juxta-articular regions.
6. Serum RF - Abnormal amounts of serum Rheumatoid factor are demonstrated by any method for which the result has been positive in fewer than 5% of healthy control subjects.
7. Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints: Osteoarthritic changes alone do not qualify.

The presence of 4 criteria supports the diagnosis of RA. Criteria 1-4 must be present for at least 6 weeks, and a physician must observe criteria 2-5. The exacerbating factors, type of onset and clinical features were recorded according to the description by the patient and the review of existing medical records. A positive family history was defined as the presence of diagnosed rheumatoid arthritis in at least one first degree relative of the patient.

The type of onset was inferred from the patient's history, supplemented by a review of the medical documents. The key points noted in this aspect were whether the disease was insidious in onset or acute in onset, whether it was polyarticular or monoarticular and whether it was symmetrical or asymmetrical involvement. Palindromic and polymyalgic types of disease onset were also enquired about. Palindromic onset was considered inpatients who reported recurrent episodes of oligoarthritis and met the diagnostic criteria for rheumatoid arthritis without any record of significant radiological erosions. Polymyalgic onset was considered in patients who reported pain and stiffness of shoulder and hip joints with proximal myalgia.

The investigations were interpreted with the following values-

1. Anaemia - Hemoglobin less than 10 gm/dl.
2. Leucocytosis-Total leucocyte count greater than 11,000 cu.mm
3. Leucopenia-Total leucocyte count less than 4,000 cu.mm
4. Thrombocytosis- Platelet count greater than 4,50,000 cu.mm
5. Raised ESR -ESR greater than 4mm in first hour in males and 10mm in first hour infemales
6. Raised CRP-CRP levels greater than 5 mg/dl for the upper limit of normal as set by the laboratory.
7. Raised serum globulin -Serum globulin level higher than the reference cut off set by the
8. Raised Alkaline Phosphatase - Serum Alkaline Phosphatase greater than 125 U/l for (or greater than the upper limit of normal set by the laboratory)

RESULTS

There were total 100 cases of RA included in the study. The maximum incidence of rheumatoid arthritis was seen in the age group of 31 – 40 years (46%) and 41-50 years (30%). It was seen that 84% cases with RA were females (84 cases) and 16% were males (16 cases).

Table 1: Clinical features of cases with rheumatoid arthritis (N=100)

Clinical features	Cases
Fever	26
Joint pain	100
Joint swelling	84
Morning stiffness	86
Deformity	74
Limitation of movements	80
Carpel tunnel syndrome	12
Generelised lymphadenopathy	10
Splenomegaly	12

Table 2: Joints involvement in Rheumatoid arthritis cases (N=100)

Joints involved	Cases
Proximal interphalangeal	96
Metacarpophalangeal	96
Wrist	66
Elbow	36
Shoulder	4
Subtalar	46
Ankle	12
Knee	12
Cervical spine	12

Table 3: Deformities in Rheumatoid arthritis cases (N=100)

Deformity	Cases
Swan neck deformity	26
Boutonniere deformity	10
Z deformity	24
Ulnar deviation of digits	40
Eversion of subtalar joints	6
Plantar subluxation of metatarsal heads	4
Hallux valgus	4

Table 4: Radiological changes in Rheumatoid arthritis cases (N=100)

Radiological changes	Cases
Juxtaarticular osteopenia	74
Soft tissue swelling	74
Joint space narrowing	60
Joint erosions	40
Intra-articular loose bodies	10
Joint subluxation	4

Table 5: Extra-articular manifestations in **Rheumatoid arthritis cases (N=100)**

Manifestations	Cases
Rheumatoid nodules	10
Mitral regurgitation	4
Sjogrens syndrome	4
Episcleritis	10
Periodontitis	4
Pleuritis	6
Coronary artery disease	4

Table 6: Blood investigations report in **Rheumatoid arthritis cases (N=100)**

Blood investigations	Cases
Anemia	66
Leukocytosis	16
Thrombocytosis	26
Raised ESR	86
Raised CRP	84
Raised alkaline phosphatase	20
Raised Serum globulin	24

The commonest clinical features noted in all the patients were joint pain (100%), and morning stiffness (86%) followed by joint swelling (84%, 84 cases), joint deformity (74%, 74 cases) (Table 1).

The commonest joint involved were proximal interphalangeal and metacarpophalangeal joints (96 cases each, 96%) (Table 2). The commonest upper limb deformity was ulnar deviation of digits (40 cases, 40%) followed by swan neck deformity (26 cases, 26%), Z deformity (24 cases, 24%), boutonnière deformity (10 cases, 10%). The lower limb deformities were eversion of subtalar joints (6 cases, 6%), plantar subluxation of metatarsal heads (4 cases, 4%), hallux valgus (4 cases, 4 %) (Table 3).

The commonest radiological changes were juxta articular osteopenia and soft tissue swelling (74%), followed by joint space narrowing (60 cases, 60%) , joint erosions (40 cases , 40%), intra-articular loose bodies (10 cases , 10%), joint subluxation (4 cases, 4%) (Table 4).

Only 34 percent in this study developed extra articular manifestations. Commonest manifestations were rheumatoid nodules (10%, 15 cases), episcleritis (10% 10cases), pleuritis (4 cases, 4%), coronary artery disease (4 cases, 4% mitral regurgitation (4 cases, 4%), sjogrens syndrome (4 cases, 4%), periodontitis (4 cases, 4%) (Table 5). Rheumatoid arthritis factor was positive in 76 % (76 cases) and Anti CCP was positive in 94% (94 cases) of the patients of rheumatoid arthritis.

The most common abnormality was raised ESR (86 cases, 86%), raised CRP (84 cases, 84%). The common abnormalities were anemia (66 cases, 66%), thrombocytosis (26 cases, 26%), raised serum globulin levels (20 cases, 20%), leukocytosis in 16% and leucopenia in 4% (Table 6).

DISCUSSION

In the present study, a positive family history of the disease in first degree relatives was noted in 28% of patients. The first degree relatives of patients with rheumatoid arthritis are at four times increased risk of developing the disease as compared to the normal population.[3] The heritability of RA, i.e., the extent to

which susceptibility to disease is explained by genetic variation in the population, has been estimated at 60%. A report on the family history of RA showed that a) 7% of the fathers of patients as opposed to 3% of fathers of controls suffered from arthritis; 15% of mothers of patients as opposed to 9% mothers of controls Suffered from arthritis b) of 2,151 brothers and sisters of patients with RA, 82 had arthritis and of 2,143 brothers and sisters of the controls 38 had arthritis. These values were found to be statistically significant.[6]

In the present study, 24% of patients reported that there exacerbation of symptoms with climatic changes requiring consultation to the physician and/or hospital admission. In these patients, it was cold weather that usually exacerbated the symptoms.[6] Smoking was a risk factor for rheumatoid arthritis in 12% of patients in this study. Smoking has been reported to be a risk factor in many study in RA.[7] Tueresson and colleagues also proposed that Smoking is one of the risk factors for extraarticular involvement of the disease.[8] Certain studies have also shown that smoking is one of the risk factors for predictor of RA primarily in the subset of patients with RA associated HLA-DRB1 genotype thus providing a classical example of the interplay between genetic and environmental factors in predisposing to RA.[7]

The predominant clinical features were joint pain, joint swelling, limitation of the joint all the patients in the study. Grassi et al reported that the commonest triad of symptoms indicted by synovitis includes pain in the joint, joint swelling and motion impairment.[9] They also reported that morning stiffness lasting at least 1 hour before maximal improvement is typical of RA.[9] Fever was reported by 26% of the patients in this study.[6]

The involvement of of joints in this study was maximum in joints of hand. The joints involved were proximal interphalangeal joints, metacarpophalangeal joints, wrist joint, and elbow joint. A review on rheumatoid arthritis published that out of 532 patients with rheumatoid arthritis, 520 patients reported involvement of the peripheral joints of hand and feet.[6] Jacoby et al also reported that in their study on 100 patients, the most commonly involved joints were metacarpophalangeal joints , wrist joint, and proximal interphalangeal.[10]

The hand deformities noticed in this study were ulnar deviation of digits (40%), swan neck deformity (26%), Z deformity (28%), and boutonniere deformity (10%). These findings can be compared to Qayyum et al in their study on 50 patients. In their studies the ulnar deviation (50%), swan neck deformity (72%), Z deformity (68%) and boutonneire deformity (80%).[11] Thus number of patients with joint deformity was lower in present study, and probably due to the shorter duration of the study period. The lower limb deformities noted in the present study were eversion of subtalar joint (6%), plantar subluxation of metatarsal heads (4%), hallux valgus (4%). The deformities reported by Qayyum and coworkers were valgus deformity (42%) and pes planus (14%).[11]

RF is one of the classical findings described in association with rheumatoid arthritis. In present RF factor was positive in 76% patients. Akil et al have reported that 80% of patients with rheumatoid arthritis are seropositive for rheumatoid factor.[1] Lindqvist et al reported that in their study on 168 cases of RA, 71% were positive for rheumatoid factor.[12] Thus, the rheumatoid factor positivity is this study is comparable to that of other studies.

Anti CCP is positive in 94% patient in this study. Its diagnostic specificity approaches 95%, so a positive test for anti-CCP antibodies in the setting of an early inflammatory arthritis is useful for distinguishing RA from other forms of arthritis. The presence of RF or anti-CCP antibodies also has prognostic significance, with anti-CCP antibodies showing the most value for predicting worse outcomes. The detection of a disease-specific autoantibody like anti-CCP could be of great diagnostic and therapeutic importance in early cases of RA while symptoms are mild.[13]

CONCLUSION

It is concluded from the present study that most common predisposing factors were family history and smoking and commonest exacerbating factor was climatic changes. The most common clinical features are morning stiffness, joint pain, joint swelling and limitation of joint movement. Extraarticulation manifestations were present in less than half of the study population. The commonest manifestations were episclerits and rheumatic nodules. Three fourth of the study population were seropositive for rheumatoid factor. Almost whole of the study population was seropositive for antiCCP antibodies.

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ORIGINAL ARTICLE

A STUDY ON CO-RELATION OF INFERTILITY AND FEMALE GENITAL TUBERCULOSIS

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ABSTRACT

Introduction: Female Genital Tuberculosis (FGTB) is an important cause of sub fertility. It can cause tubal obstruction and dysfunction, impair implantation due to endometrial involvement and rarely lead to ovulatory failure.

Objective: To evaluate the rate of female genital tuberculosis and its presentational symptoms in patients of infertility, to study the genital tuberculosis by hystero-laparoscopy and different methods available for its diagnosis including PCR technique and histo-pathological examination and to study conception rate after ATT(Anti tubercular treatment) in positive cases of PCR.

Methodology: This was a prospective observational study conducted in the Department of Obstetrics and Gynecology, SMIMER, Surat, on 54 subjects from May 2007 to December 2009. Patients of reproductive age group from 18 years to 36 years with the duration of infertility of more than 2 years were included.

Results: Out of 54 subjects, cases of primary infertility were 44 (81.5%) and secondary infertility were 10 (18.5%). Chronic pelvic pain in 16 patients (29.6%) was the most common associated complaint apart from infertility. On investigation ,cases found positive were 19 by PCR from endometrial biopsy, 22 cases (40.7%) by laparoscopy, 2 cases (3.7%) by histology and 3 cases (5.6%) by hysteroscopy. 19 cases were given ATT, out of those 6 cases (31.6%) had conceived.

Conclusion: Infertility is one of the most common symptoms of FGTB and more cases of genital TB would be diagnosed in patient of infertility in endemic areas.

Keywords: Female genital tuberculosis (FGTB), Infertility, Anti tuberculosis treatment (ATT), Polymerase chain reaction (PCR)

Abbreviations: Female genital tuberculosis (FGTB, Anti tubercular treatment (ATT), Polymerase chain reaction (PCR), Erythrocyte sedimentation rate (ESR), Tuberculosis (TB), Histo pathological examination (HPE)

INTRODUCTION

Female genital tuberculosis affects about 12 % of patients having pulmonary tuberculosis.[1].The prevalence of FGTB in infertility clinics shows marked variation ranging from 15% to 25%.[2] It is involved in about 5 -16 % cases of infertility among Indian women. [3 ,4 ,5.] In 80 -90 % of cases, FGTB affects young women of 18 -38 years of age and is an important cause of infertility.[2, 6.]The most common mode of transmission to the genital tract is through haematogenous spread from lungs ,other sites being kidney and intestine.[7] The fallopian tubes (92-100%) are the most commonly affected genital organs, followed by endometrium(50%),[2] ovary(10-30%), cervix(5%) and vulva and vagina(<1%).According to Novak's,[8] the tubes are already affected when the diagnosis of tubercular endometritis is made. The characteristic feature is the presence of yellowish-grey tubercles on the peritoneal surface of the tubes and mesosalpinx with fimbrial end of tube remaining open in half the cases.[9] Endometrial appearance may be unremarkable initially but may end up in Asherman's syndrome leading to secondary amenorrhea.

Infertility is one of the commonest presentations of genital TB. Other clinical symptoms & signs can be fever, anorexia, menstrual disorders ranging from menorrhagia to amenorrhea, chronic pelvic pain, abnormal vaginal discharge, urinary or defecation problems, lymphadenopathy, abdominal masses, ascites,

doughy feel of abdomen, fornix tenderness, TO masses etc.

Diagnosis of FGTB is often limited to clinical suspicion. A pelvic USG is of help in presence of TO masses. Definitive diagnosis of FGTB is possible only by the isolation of Mycobacterium tuberculosis bacteria from genital tract or histological demonstration of granuloma. The material taken for culture or biopsy is the endometrium and menstrual discharge.[10] The best time for collecting endometrial sample is several days before expected menses when tubercles reach maximum growth. The polymerase chain reaction (PCR) is a rapid method for detection & quantification of few DNA copies with high sensitivity & specificity, the results being available in 1 day. PCR may be positive with only 1-10 organisms /ml.[11]On hysteroscopy , no classical features are described but intrauterine adhesions, scarring or narrowing of cavity may be found.

Short - course chemotherapy (DOTS) for 6-9 months has been found to be effective for medical treatment of FGTB.[12, 13]. The chances of pregnancy in females suffering from genital TB have so far been poor (5%) even after completion of treatment.[14]

METHODOLOGY

This prospective observational study was conducted in the Dept. of Obstetrics & Gynecology, SMIMER, Surat, from May 2007 to Nov 2009. All infertility patients fulfilling the inclusion criteria reported during the study period were included in the study. Inclusion criteria were: a)Reproductive age group female from 18 years to 36 years; b) Medically fit patients; c) Infertility duration should be more than 2 years; and d) at least 3 times ovulation induction with follicular monitoring done in past. Subjects were selected from patients visiting infertility clinic with the written consent.

On admission, subject's detailed history (menstrual, obstetrical, past, medical & familial) was taken and thorough general examination, systemic, gynecological examinations were carried out. Routine investigations were done including CBC, blood group, RFT, RBS, ESR, CXR, urine routine & microscopy, &HIV, HBsAg, VDRL Informed consent was taken from all patients.

All enrolled patients underwent diagnostic hysterolaparoscopy to look for the status of fallopian tubes, presence of any granulations, caseation or adhesions over tubes or uterus. In all patients, endometrial biopsy was taken especially from both cornual ends & sent for histological examination in formalin &for PCR analysis in normal saline solution respectively to the lab immediately.

After confirmation of diagnosis of genital TB, ATT was started. DOTS (category-1) were given to all patients with positive PCR. Treatment was given in 2 phases- **initial phase(2 months)**- isoniazide, rifampicin, pyrazinamide & ethambutol along with vitamin B6 were given**, continuation phase-(4 months)** – isoniazide &rifampicin were used**.** Patients were followed for two years for conception. In order to improve pregnancy rates intrauterine insemination (IUI) was done in some patients. Statistical analysis was carried out using SPSS sum & Chi square test. The study was approved by institutional ethical committee.

RESULTS

Total 54 patients were included in the study. Out of 54 subjects, 46(86.2%) were in age group between 20 to 30 years, with mean age of 26.33 years. 44(81.5%) cases had primary infertility & 10(18.5%) had secondary infertility. In present study, there was positive history of extra genital TB in past in 11(20.3%) cases and family history was positive in 13(24%) cases. The patients were considered to be FGTB positive or negative on basis of diagnostic methods used in alone or in combination. In present study significant association has been found between positive past history and laparoscopic findings statistically. Out of 11 cases of positive past history, laparoscopy showed positive findings in 8 cases (72.7%).

Table 1: Co-relation between PCR and past history

Past history	PCR for Tuberculli		Total
	Negative	Positive	
Absent	31(72.1)	12(27.9)	43
Present	4(36.4)	7(63.6)	11

As shown in Table - 1, significant association has been found between negative past history & negative PCR. Out of 11 cases with positive past history, 7 cases (63.6%) were PCR positive for genital TB, while out of 43 cases with negative past history 31(72.1%) were PCR negative for genital TB.

Table 2: Distribution of associated signs and symptoms (n=54)

Symptoms	No. (%)
Chronic pelvic pain	16 (29.6)
Irregular period	15 (27.7)
Vaginal discharge	14 (25.9)
Scanty menses	12 (22.2)
Pelvic mass	6 (11.1)
Dysmenorrhea	2 (3.7)
Amenorrhea	00

Table - 2 shows that on history and examination chronic pelvic pain was found in 16 patients (29.6%), irregular menses in 15 patients (27.7%), vaginal discharge in 14 cases(25.9%), scanty menses in 12 patients(22.2%), pelvic mass in 6 patients(11.1%), and dysmenorrhoea in 2patients(3.7%).Not even a single case of amenorrhea (primary or secondary) was found in our study.

Out of 16 cases of chronic pelvic pain, 10 cases (62.5%) had positive PCR, 6 cases (37.5%) had positive laparoscopy and only 1 case (6.2%) has positive hysteroscopy for FGTB. Thus PCR may be the most sensitive method to diagnose FGTB in clinically suspected women especially those who have h/o chronic pelvic pain. In 14 cases of vaginal discharge with infertility, 10 (71.5%) cases were negative for FGTB. In 6 cases 0f pelvic mass, 5(83.3%) cases were positive by both PCR as well as laparoscopy. In 12 cases of scanty menses, laparoscopy was positive in 9(75%), PCR was positive in 4(33.3%), hysteroscopy was positive in 1(8.3%) and HPE was positive in 1(8.3%) case. In 15 cases of irregular menses, 6 cases (40%) of positive PCR, 5 cases (33.3%) of positive laparoscopy and only 1 case of positive hysteroscopy & HPE were found. In 2 cases of dysmenorrhoea, PCR was positive in both cases and laparoscopy was positive in 1 case.

Table 3: Comparison of the diagnosis yield of genital tuberculosis by different methods (N=54)

Test	Female Genital Tuberculosis	
	Positive (%)	Negative (%)
PCR	19 (35.2)	35 (64.8)
HPE	2 (3.7)	52 (96.3)
Laparoscopy	22 (40.7)	32 (59.3)
Hysteroscopy	3 (5.6)	51 (94.4)
Dye test	20 (37.0)	34 (63.0)

Table - 3 shows that among the 54 patients suspected of suffering from FGTB, 21 were confirmed to have the evidence of M. tuberculosis infection by either HPE 2 (3.7%) or PCR 19 (35.2%). 22 cases (40.7%) were positive in laparoscopic findings which included tubercles on peritoneum, ovary, TO masses, caseous nodules, encysted ascites, pelvic adhesions, hydrosalpinx, pyosalpinx, beaded tubes etc. Only 2 cases (3.7%) showed typical classic features on HPE like caseous necrosis, Giant cells, epithelial cell clusters and lymphocyte infiltration. On hysteroscopy only 3 cases (5.6%) were positive for FGTB in which 1 case had pale endometrium, 1 case had intrauterine adhesion and 1 case had granular lesion at cornual region.

On laparoscopy during dye test done by methylene blue, 20 cases (37%) out of 54 were considered positive for FGTB who had either unilateral block, bilateral block or delayed spillage.

Table 4: Correlation of ATT and pregnancy rate on follow-up

ATT	Conceived	Not conceived	Total
Given	6(31.6)	13(68.4)	19
Not given	3(8.6)	32(91.4)	35

In this study out of 19 cases of positive PCR, 13 cases (68.4%) were found positive on laparoscopy, 6 cases (31.5%) found positive on dye test, and hysteroscopy & HPE were positive in only 1case(5.3%).Here statistically significant association was found between laparoscopy and PCR technique to detect FGTB. (p=.002) . There were also statistical association found between laparoscopy& dye test (p=0.001), it means if the tubes were not damaged grossly on laparoscopy, in majority of cases normal bilateral free spillage was present.

Out of 54 cases, 19 cases who were PCR positive were given ATT for 6months according to DOTS. Table - 4 shows that out of 19 treated cases, 6 cases (31.6%) conceived on follow up spontaneously or with other assisted techniques like ovulation induction or intrauterine insemination, while 13 didn't conceive even after 1 year of follow up. But out of 35 cases that were not given treatment, 3 cases (8.6%) conceived spontaneously. Of these 6 cases who conceived after ATT, 4 cases became pregnant within 6 months of starting treatment and 2 cases conceived after 6 months.

DISCUSSION

In present study maximum patients 46(85.2%) were in age group of 20 to 30 years. Statistically significant association had been found between age and infertility specially primary infertility .Mean age in our study was 26.3 years which was comparable to studies of Roya rozati et al[15]& N Gupta et al[16].In our study ,11 cases(20.3%) had positive H/o extra genital TB and 13 cases(24%) had family H/o TB. In contrast to present study, U N Jindal et al[12] found positive past history in 73.5% cases & positive family history in 10.1% of infertile patients. Chronic pelvic pain in 16 patients (29.6%) and irregular menses in 15 patients (27.7%) were the most common symptoms in patients apart from infertility. In our study we found that most of these symptomatic patients were found positive on PCR & laparoscopy for FGTB.

As far as diagnostic test were concerned, out of 54 subjects suspected of suffering from FGTB, 19 cases(35.2%) were positive on PCR, 22 cases(40.7%) were positive on laparoscopy, 2 cases(3.7%) were positive on HPE and 3 cases(5.6%) were positive on

hysteroscopy. Our results depicted that PCR is the best method of diagnosing FGTB and a combination of PCR and laparoscopy is totally dependable for the diagnosis. In clinically suspected symptomatic cases, PCR could be the technique of choice for its higher sensitivity and specificity. Hysteroscopy and HPE were found non specific. There was also statistical association found between laparoscopy& dye test (p=0.001), it means that if the tubes were not damaged grossly on laparoscopy, in majority of cases normal bilateral free spillage was present.

In present study 19 cases were given ATT out of which 6 cases (31.6%) conceived, 4 of which got pregnant within 6 months of starting ATT. Most of these conceived patients had positive PCR test and maximum number of these cases were having negative (normal) dye test(i.e. 3 out of 4). So when tubes were found grossly damaged on laparoscopy &/or dye test, conception rate was very poor but the patient of FGTB found in early stages by PCR, and where the laparoscopy and dye test were normal, conception rate was very good. Sin SY et al studied that if patients are adequately treated before tubes are irreversibly damaged, chance of successful pregnancy is reasonably good with 20% pregnancy rate reported.[17]

CONCLUSION

Infertility is one of the commonest symptoms of FGTB and more cases of genital TB would be diagnosed if this disease is considered in evaluation of every patient of infertility in areas where TB is endemic. PCR represents a rapid and sensitive method for detection of mycobacterium DNA in early FGTB cases. The patients of FGTB found in early stages by PCR and where laparoscopy and dye tests are normal, ATT can improve the conception rates.

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ORIGINAL ARTICLE

EVALUATION OF EFFECTIVE MANAGEMENT OF SEPSIS IN EMERGENCY DEPARTMENT IN SUEZ CANAL UNIVERSITY HOSPITAL, EGYPT

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ABSTRACT

Introduction: Sepsis is a syndrome has especial characters by systemic inflammation due to infection. There is a severity ranging from sepsis to severe sepsis and septic shock. More than 1,665,000 cases of sepsis diagnosis in the United States each year, with a mortality rate of 50%. Interventions to be completed within 6 hours of triage are better to use vasopressors, measure of CVP and ScvO2, and use of targets for quantitative resuscitation. Emergency physicians performance improvement efforts to improve patient outcomes in severe sepsis.

Aim: To improve the outcome in patients with sepsis attending emergency room in Suez Canal University in the period from 1-11-2014 to 1-4-2015.

Methodology: Descriptive study, where every case of sepsis presented to the department of Emergency medicine at Suez Canal University Hospital that met the inclusion criteria, had been included in the study

Results: This study revealed that the mean age of studied patients was 66.38± 13.34 with a wide range of (28-90). Our study showed that (88%) of the patients received antibiotic within the first three hours. none of them obtained blood culture. (81%) of the patients received fluid resuscitation therapy within the first three (65.5%) of them received ≥ 30 mL/kg loading fluid within 3 hours of sepsis diagnosis.

Conclusion: The results revealed adherence of ER physicians to guidelines at Emergency Department in Suez Canal University Hospital. Most of the studied patients followed the SSC guidelines.

Keywords: Management**,** sepsis, SIRS.

INTRODUCTION

Sepsis is a syndrome characterized by a systemic inflammatory reaction to infection. There is a severity range from sepsis to severe sepsis and septic shock. More than 1,665,000 cases of sepsis occur in the United States each year, with a mortality rate of 50 %.[1]

Uniform definitions developed over years from the sepsis syndrome, including the systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis and septic shock. SIRS characterized by the clinical aspects derived from an acute yet nonspecific illness, whereas an infectious etiology is required for the diagnosis of sepsis. As sepsis progresses, organ system dysfunction becomes obvious (severe sepsis) with the end development of fluid refractory cardiovascular dysfunction (septic shock).The 2012 Surviving Sepsis Campaign which includes a sepsis care bundle. Interventions to be completed within 3 hours of triage include measuring lactate levels, obtaining blood sample for cultures before giving broad-spectrum antibiotics (within 45 minutes), and giving 30 mL/kg of crystalloid for hypotension or for lactate levels at least 4 nmol/L.[2]

Interventions to be completed within 6 hours of triage are better to use vasopressors, measurement of CVP and ScvO2, and use of targets for quantitative resuscitation. Emergency physicians' performance improvement efforts to improve patient outcomes in severe sepsis.[2]

Sepsis is a syndrome has especial characters by systemic inflammation due to infection. There is a severity ranging from sepsis to severe sepsis and septic shock,Interventions to be completed within 6 hours of triage are better to use vasopressors, measure of CVP and ScvO2, and use of targets for quantitative resuscitation. Emergency physician's performance

improvement efforts to improve patient outcomes in severe sepsis.[1]

METHODOLOGY

This descriptive study included 32 patients attended emergency room in Suez Canal university hospital that with the following inclusion criteria: Adult,≥ 18 years , both sexes, diagnosed to have SIRS according to SSC guidelines: Hyperthermia more than 38.3°C or Hypothermia less than 36°C, tachycardia more than 90 bpm, leucocytosis (more than 12,000 μL-1) or Leukopenia (less than 4,000 μL-1) or >10% bands , tachypnea more than 20 bpm , diagnosed to have sepsis according to SSC: SIRS + infection, diagnosed to have severe sepsis according to SSC: sepsis with signs of organ dysfunction or organ hypo-perfusion: Hypotension (<90/60 or MAP <65), lactate more than 2, areas of mottled skin or capillary refill more than 3 seconds, creatinine more than 2.0 mg/dl, disseminated intravascular coagulation (DIC), platelet count less than 100,000

Acute renal failure or urine output less than 0.5 ml/kg/hr for at least 2 hours, hepatic dysfunction as evidenced by Bilirubin more than 2 or INR more than 1.5, cardiac dysfunction, acute lung injury or ARDS & diagnosed to have septic shock according to SSC: severe sepsis associated with refractory hypotension (BP<90/60) despite adequate fluid resuscitation and/or a serum lactate level more than 4.0 mmol/L. With exclusion criteria of children, patient known to have end organ failure, patients refused to be included in this study & immunocompromised patients or history of suppressive therapy.

Data was collected in pre-organized data sheet by the researcher; the following was performed to all included patients: Full history: with the prepared questionnaire which include data regarding age, gender, past medical history, evidence of recent infection. Clinical evaluation of the patients was be carried out on arrival to Emergency Department regarding general status, vital signs. Investigations: Laboratory investigations: hemoglobin, hematocrit, platelet count ,total white blood cells, prothrombin time, international normalized ratio, AST, ALT, bilirubin , creatinine levels ,blood urea, serum electrolytes, acetone, random blood sugar, arterial blood gases, blood culture, urine analysis and culture .Radiological investigations: chest X-ray, pelvic-abdominal ultrasound, echocardiography if needed & ECG.Then follow up was carried out: Hourly: Blood pressure, IV fluid regimen, Urine output ,Symptoms & clinical signs as vomiting, abdominal pain, hypovolemia, fever, the level of consciousness. Then, outcome: Clinically, laboratory, site of admission (inpatient or ICU). This study performed after accepted from ethical committee in faculty of medicine, Suez Canal University, Ismailia, Egypt and all patients were written consent for participants in this study.

RESULTS

This study revealed that the mean age of studied patients was 66.38± 13.34 with the wide range of (28-90). Our study revealed that the percentage of females with sepsis is more than males. In our study clinical variables were: heart rate (beat/ min) mean 106 (65-140) Respiratory rates (breaths/min) mean 21.75±5.66 (12-32). Temperatures (c) mean 38c (35-40). Blood pressures (mm Hg) mean 85 (130-40).

Table 1: Outcome of patients following or not following the guidelines

Guidelines	Outcome	
	Improved	Deteriorated
Follow	12	16
Not Followed	0	4

Table 2: Outcome of studied patient according to the start time of IV fluid therapy

Timing of IV Fluids infusion	Outcome	
	Improved	Deteriorated
Within the 1st 3 hrs	12	14
More than 3 hrs	0	4

Table 3: Outcome of studied patient according the amount of fluid infused

Total amount of IV fluids infusion in ml	Outcome	
	Improved	Deteriorated
30ml/kg	10	11
20ml/kg or less	0	9

Table 4: Distribution of patients according to the source of infection

Source of infection	Percentage
Chest	44%
Abdomen	6%
Urinary Tract	19%
Infected Wound	22%
Not Known	9%

Table 1shows that by following the guidelines 12 patients were improved and 16 patients were deteriorated. The table also shows that all patients that didn't follow the guidelines deteriorated.

Table 2 shows that 12 of the patient that started treatment within the 1st three hours of presentation improved while 14 of them deteriorated, and shows that all patients that started fluid therapy after 3 hours deteriorated.

Our work revealed that the most common sources of infection were lung 44%, skin 22%, urinary tract 19%, abdomen 6% and unknown source presenting 9%.Our study showed that 64% of septic shock patients improved after treatment in the emergency department. Our work showed the outcome of the patients according to their presenting complaints and it was as the following: 87.5% of the patients presented with DLOC deteriorated, 43% of patients with poor oral feeding deteriorated. Our study shows that 66.6% of septic patients with diabetes deteriorated.

Table 3 shows that 10 of patient that follow the guidelines improved while 11 of them deteriorated and show that all of patients that didn't follow the guidelines deteriorated.

Our study showed that 58.8% of hypertensive patients with sepsis deteriorated in an emergency department. Our study showed that (88%) of the patients received antibiotic within the first three hours.non of them obtained blood culture. (81%) of the patients received fluid resuscitation therapy within the first three (65.5%) of them received ≥ 30 mL/kg initial fluid challenge within 3 hours of sepsis diagnosis.In our study 12 patients improved after management at ER &20 patients deteriorated, 12 of studied patients followed the guidelines improved, all patients have not followed the guidelines deteriorated which were 4 patients in our study .This reflects the importance of the strict application of guidelines.

Table 4 shows that chest infection was the most common source of infection in sepsis patients was the chest (44%)

DISCUSSION

This study revealed that the mean age of studied patients was 66.38± 13.34 with a wide range of (28-90). That was matching another study that revealed that the mean age was 63.8 +/- 18.5. [3]

Our study revealed that the percentage of females with sepsis is more than males and this result wasn't matching another study which revealed that the incidence of sepsis is higher in men (54%) than women (46%).[4]

In our study clinical variables were: heart rate (beat/min) mean 106 (65-140) Respiratory rates (breaths/min) mean 21.75±5.66 (12-32). Temperatures (c) mean 38c (35-40). Blood pressures (mm Hg) mean 85 (130-40). which was closely matching another study that revealed Clinical variables, median (IQR) Heart rate (beats / min) 109 (96–122) Respiratory rate (breaths / min) 20 (20–25) Temperature (C) 38.3 (37.4–39.0) Blood pressure, mean arterial, mm Hg (IQR) 87 (78–98) .[5]

Our work revealed that the most common sources of infection were lung 44%, skin 22%, urinary tract 19%, abdomen 6% and unknown source presenting 9%. That wasn't matching another study that revealed that the most common site of infection was urinary tract, Lung, and skin were the most common infected sites (34.3, 14.0, and 13.8%, respectively). [5]

Our study showed that 64% of septic shock patients improved after treatment in the emergency department, that wasn't matching another study that revealed 75.2% improvement in septic shock patients. [6]

Our work showed the outcome of the patients according to their presenting complaints and it was as the following: 87.5% of the patients presented with DLOC deteriorated, 43% of patients with poor oral feeding deteriorated. Another study showed that approximately one-third of patients with sepsis had a Glasgow coma scale less than 12 and that confused and the low conscious level was an independent prognosis factor, increasing mortality rate to 63% when Glasgow coma scale below 8.[7]

Our study shows that 66.6% of septic patients with diabetes deteriorated while another study stated that deterioration was equal in diabetic and nondiabetic patients (31.4% vs. 30.5% respectively). [8]

Our study showed that 58.8% of hypertensive patients with sepsis deteriorated in an emergency department. While other studies revealed that hypertension is protecting against deterioration in septic patients as an increase in the occurrences of sepsis (from 82.7 to 240.4 per 100 000 population), and a decrease in the mortality rate of patients (from 27.8 % to 17.9 %), has been reported in the USA, from 1979 through 2000. The prevalence of hypertension in the same population was >7.0 % to 18.6 % in the same period. [9]

Our study showed that (88%) of the patients received antibiotic within the first three hours. none of them obtained the blood sample for culture. (81%) of the patients received fluid resuscitation therapy within the first three (65.5%) of them received ≥ 30 mL/kg initial fluid challenge within 3 hours of sepsis diagnosis. Another study showing the compliance of SSC guideline application revealed that only 40% (32/80) of patients received antibiotics within one hour of diagnosis. Two sets of blood cultures were obtained before antibiotic administration in 94% (78/83) of patients. (James and Cheryl, 2013). [10]

Nearly all patients (n=81; 97.6%) received at least 1 liter of fluid within 6 hours of sepsis diagnosis. Almost half of the patients (49.4%) received ≥ 30 mL/kg fluid loading within 3 hours of sepsis diagnosis. (James and Cheryl, 2013). [10]

In our study 12 patients improved after management at ER &20 patients deteriorated ,12 of studied patients followed the guidelines improved ,all patients have not followed the guidelines deteriorated which were 4 patients in our study .This reflects the importance of the strict application of guidelines.

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ORIGINAL ARTICLE

STUDY OF CHANGE IN MACULAR VOLUME WITH UNCONTROLLED HBA1C LEVELS IN A DIABETIC PATIENT IN ABSENCE OF DIABETIC MACULAR OEDEMA

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ABSTRACT

Aim: Our aim of this study was to analyze the beneficial effects (if any) of music therapy in decreasing anxiety, providing stable haemodynamics and decreasing anaesthetic agent requirement in patients coming for modified radical mastectomy.

Methods: Forty patients in the age group of 40 -50 years scheduled for modified radical mastectomy were selected for this prospective observational study. They were randomly assigned to Group M (receiving music therapy) and Group N (not receiving music therapy). Musical intervention was started one hour prior to surgery. The level of anxiety (score of 1 to 4, based on simplified version of state-trait anxiety inventory), pulse rate, MAP were recorded at 15 minutes interval up to one hour post surgery and compared with their baseline values.

Results: With musical intervention, anxiety score declined to 2 in 80 % of cases at the time of induction and in Group N no such improvement was observed. Postoperatively, level of anxiety decreased in Group M was 100 % displaying a score of 1. Group M patients also displayed stable haemodynamics throughout the perioperative period. However, in Group N, there was a significant increase in both pulse rate and MAP intraoperatively ($p < 0.0001$). The need for anaesthetic agent (isoflurane) was also more in the control group compared to Group M ($p = 0.05$ and 0.0250 at 15 minutes and 1 hour after incision respectively).

Conclusion: Music therapy has the potential to be an alternative cheap and promising option to pharmacological premedication agents which needs to be looked in to.

Keywords: Breast cancer, music therapy, peri-operative, hemodynamics

INTRODUCTION

The very thought of the operation theater (OT) brings a lot of uneasiness to common people. Just the initial idea of having surgical procedures can bring about very high levels of anxiety in patients.[1]This is more so for cancer patients who are scheduled for surgery. The typical OT ambience with the sound of the monitors, the instruments, and the discussion of the medical staff by the side of the patient leads to a lot of stress and anxiety to the patient awaiting surgery which can lead to unstable haemodynamics (tachycardia, high blood pressure), increased intraoperative blood loss, impaired wound healing, increased risk of infection, and may complicate the induction of anaesthesia and impede postoperative recovery.[1, 2] Anxiety has also been proven to cause higher analgesic and anaesthetic requirement, postoperative pain, and prolonged hospital stay,and thus, an overall unfavourable surgical outcome.[3]

Though numbers of drug are being used as part of premedication to reduce this anxiety, they have their own drawbacks in terms of side effects. There is increasing interest in evaluating the use of nonpharmacological interventions such as music to minimize potential adverse effects of anxiety-reducing medications.[4] The attenuation of perioperative stress through music listening is probably due to the activation of emotional and cognitive processes that evoke feeling of pleasure and can distract patient's attention from fear and unpleasant thoughts related to the surgical procedure. Few investigators have got beneficial results with music intervention in the perioperative period in both adults and children. [4, 5, 6, 7, 8] Further

research into music therapy is warranted in light of the low cost of implementation and the potential ability of music to reduce perioperative patient distress. [7] This has prompted us to study the effect of pre recorded music on the level of anxiety, anaesthesia requirement, perioperative haemodynamics and the need for hypotensive agents in patients undergoing modified radical mastectomy (MRM).

METHODOLOGY

This study was conducted in the department of Anaesthesiology, Dr. B.Borooah Cancer Institute and Research centre, Guwahati in the period between Jan'15 and Dec'15 after getting approval from the institutional review board. This was a prospective observational study. 40 Normotensive patients of carcinoma (CA) breast in the age group of 40-50 years with no associated morbidity who are scheduled for modified radical mastectomy (MRM) were selected for this study. After properly explaining the nature of the study and obtaining informed written consent of the patients, the patients were randomly included in either Group M (receiving musical intervention) or Group N (no musical intervention) i.e. the control group. While giving clearance for anaesthesia, the patient's were asked about their choice of music and was recorded in the pre-anaesthesia check up form. On the day of surgery, the patients were brought to the operation theater (OT) waiting room 1 hour prior to surgery. Their vitals [pulse, blood pressure (BP), mean arterial pressure (MAP)] and the level of anxiety were recorded. Anxiety was recorded on a 4 point scale which is based on a simple version of the state-trait anxiety inventory. [9]The 4-point A-State intensity response scale is as follows: 1 = not anxious at all; 2 = somewhat; 3 = moderately so; 4 = Very much so.They were then premedicated with inj. Midazolam 1mg IV. Following this, Group M patients were made to listen to the music of their choice using a headphone. This was continued throughout the surgery till the time of extubation. Headphones were used so as to avoid the patients from hearing ambient sounds and also to avoid other patients getting disturbed. Group N patients were not provided with any music and were kept in the same waiting room as Group M. The vitals and the anxiety levels were recorded every 15 minutes till the patients were shifted to the OT table and additional premedications (no anxiolytics) were given (on the OT table). Pulse, BP, MAP [diastolic pressure plus one third (systolic-diastolic)] were continued to be recorded during induction of anaesthesia, laryngoscopy and endotracheal intubation and throughout the surgery at 15 minutes interval till extubation. Anaesthesia was maintained with O_2, N_2O and isoflurane (with BIS monitoring) and muscle relaxation was maintained with inj. Vecuronium bromide. The percentage (volume %) of isoflurane needed to maintain acceptable BIS and MAP within 20 mmHg of the baseline value was recorded and Injection nitroglycerine (NTG) infusion was used as the rescue hypotensive agent to keep the MAP within 20 mmHg of the baseline value (if it was not maintained with isoflurane up to 1.2 volume % alone). Intraoperative hypotension or hypertension is defined as increases or decreases of ≥ 20 mmHg in the MAP from the patient's preoperative MAP.[2] Our target was to maintain the MAP within this range as fluctuations beyond this is associated with increased incidences of postoperative complications.[10] This target of MAP was based on the physiology of autoregulation of regional circulations and the impact of anaesthesia and surgery on autoregulation.[10, 11, 12] Once the patients were adequately reversed and extubated, the Group M patients were again made to listen to the music which was stopped just prior to extubation. Vitals and anxiety levels were continued to be recorded at 15 minutes and 1 hour interval respectively for 6 hours post operation.

Statistical Analysis

Data were expressed as Mean ± Standard Error of Mean (SEM). The significance of the level of anxiety, pulse rate, MAP etc. were compared to the baseline values of the said parameters and was determined by applying ONE WAY ANOVA followed by Dunnet's multiple comparison tests. Student "t" test was used to see the differences among music and non music group at different point of time. P values of < 0.05 were considered to be statistically significant.

RESULTS

All the patients under study had significant anxiety while coming for PAC. No patient had an anxiety score of less than 3. 47.5% patients had an anxiety score of 4 and the rest had a score of 3. After starting musical intervention in Group M, this anxiety level started to decline to a score of 2 in 60% of patients within 15 minutes and then in another 30 minutes time, i.e. at 45 minutes, the number of patients with a score of 2 increased to 90% and at induction also significant number of patients had a score of 2 (80%). However, in Group N, no such decline in the anxiety level was observed. On the contrary, fraction of patients with a score of 4 increased to 70% in 15 minutes which remained so till induction. Musical intervention did result in significant reduction of anxiety preoperatively which was not observed in the control group. Postoperatively, we observed substantial decrease in the anxiety level in Group M patients. At 15 minutes after extubation, 60% had a score of 2 and the rest 40% had a score of 1, i.e. no anxiety and after 1 hour of extubation, all the patients in the group displayed no anxiety (score

1). In the control group also, we observed a decrease in the anxiety level postoperatively compared to the baseline state with 65% displaying a score of 2 and the rest 35% a score of 3 at 15 minutes after extubation which further decreased to a score of 2 after 1 hour of extubation. So, postoperatively there was a decline in the anxiety level in both the groups, however, this was more so in the musical intervention group.

Table 1: Pulse, MAP and Level of anxiety up to induction

	Pulse	MAP	Level of Anxiety (n = 20)			
			1	2	3	4
Baseline						
Group M	85.10±1.938	90.30±0.9655	0	0	50%	50%
Group N	85.00±1.606	85.50±0.7931	0	0	55%	45%
15 Min after music intervention						
Group M	76.70±1.079^{xxx}	87.10±0.9567	0	25%	75%	0
Group N	87.70±1.154	99.50±1.846^{XXX}	0	0	30%	70%
30 Min after music intervention						
Group M	71.90±0.8395^{XXX}	99.50±1.846^{XXX}	0	60%	40%	0
Group N	86.30±0.9208	99.50±1.846^{XXX}	0	0	30%	70%
45 Min after music intervention						
Group M	72.10±0.8269^{XXX}	85.70±1.300^{XX}	0	90%	10%	0
Group N	85.30±0.9545	102.1±1.244^{XXX}	0	0	30%	70%
During Induction						
Group M	73.40±1.206^{XXX}	83.30±0.8114^{XXX}	---			
Group N	87.20±0.8000	96.00±1.105^{XXX}				
P value						
Group M	F = 19.6P < 0.0001	F = 6.450P < 0.0001	---			
Group N	F=1.082P = 0.3710	F = 25.13P < 0.0001				

^{x} = p < 0.05; ^{xx} = p < 0.001; ^{xxx} = P < 0.0001, level of anxiety: 1=not anxious at all; 2=somewhat; 3=moderately so; 4=Very much so

Table 2: Intra-operative Pulse, MAP, average volume% (vol %) of isoflurane, NTG requirement

	Pulse	MAP	Vol % of Isoflurane		NTG requirement
Baseline					
Group M	85.10±1.938	90.30±0.9655	---		---
Group N	85.00±1.606	85.50±0.7931			---
During intubation					
Group M	80.50±1.305	86.40±0.8026^{X}	0.6 %		---
Group N	88.90±0.9116	100.9±1.288^{XXX}	0.6 %		---
15 min after incision					
Group M	72.50±1.247^{XXX}	83.90±1.061^{XXX}	0.64±0.04724	P = 0.05	---
Group N	88.90±0.9116^{XXX}	99.90±1.844^{XXX}	0.78±0.0521		---
1 hour after incision					
Group M	73.80±1.015^{XXX}	83.50±1.123^{XXX}	0.61±0.3692	P = 0.0250	---
Group N	92.6±1.274^{XXX}	96.70±1.008^{XXX}	0.80±0.07255		35 %
P value					
Group M	F =17.33P < 0.0001	F = 9.861P < 0.0001	---		---
Group N	F = 6.351P < 0.0001	F = 29.67P < 0.0001			

(^{x} = p < 0.05; ^{xx} = p < 0.001; ^{xxx} = P < 0.0001, NTG = Nitroglycerine)

As regarding haemodynamics, all the patients under study in Group M displayed stable pulse and MAP throughout the perioperative period. Compared to the baseline, Group M patients had greater reduction (p < 0.05) in the pulse rate and MAP till induction (Table 1) [mean ± SEM: 85.10±1.938 (pulse); 90.30±0.9655 (MAP) at baseline against 72.10±0.8269^{XXX} (pulse); 85.70±1.300^{XX} (MAP) at 45 minutes and 73.40±1.206^{XXX} (pulse); 83.30±0.8114^{XXX} (MAP) at induction]. Intraoperative MAP was maintained within the target range with isoflurane alone without the need for NTG in any of the cases. Intraoperatively as well as postoperatively also, Group M patients had greater reduction (p < 0.05) in pulse and MAP compared to the baseline (Table2, 3).

In the control group, i.e. Group N, however, though heart rate was maintained below 100 per minute in the preoperative period (heart rate changes were not statistically significant preoperatively) there was an increase in the heart rate to more than 100 per minute in the intraoperative period (including extuba-

tion) in 45% of the cases ($p < 0.0001$). 66.6% of these cases, however, were on NTG infusion to maintain MAP within the target level and the increased heart rate in these cases might be because of the effect of NTG. As is seen with the heart rate, we observed a similar increase in the MAP to more than 20 mmHg of the baseline values in 60% of the cases preoperatively (including induction). This trend was maintained during laryngoscopy and endotracheal intubation where 35% patients displayed increase of MAP to more than 20 mmHg of the baseline values. In the intraoperative period also, in this fraction of patients MAP remained above the target level even with 1.2% isoflurane and NTG infusion had to be started to maintain the MAP. Post extubation, however, the MAP was maintained within the acceptable limit in all the cases under study in the control group. Statistically significant rise of MAP ($p < 0.0001$) was seen throughout the preoperative, intraoperative period and up to 15 minutes post extubation in the control group (Table 1, 2, 3). Though increase in the pulse rate was not statistically significant in the preoperative period but intraoperatively up to the time of extubation rise in pulse rate observed was highly significant ($p < 0.0001$) (Table 2,3). In intergroup comparison also, control group had significantly higher ($p < 0.001$) pulse rate and MAP throughout the perioperative period (Table 4). Musical intervention thus resulted in stable haemodynamics in the perioperative period which was not observed in the control group.

As haemodynamics was well maintained throughout the perioperative period in Group M, we didn't need to use NTG in any of the cases and the anaesthetic requirement was also less in this group of patients where we didn't had to increase the isoflurane concentration to more than 1% in any of the cases. But in the control group, we had to use NTG infusion in 35% of cases in the intraoperative period where the upper limit of 1.2% isoflurane couldn't maintain the MAP in the desired range. So the anaesthetic and hypotensive agent requirement was more in the control group compared to the musical intervention group.

Table 3: Pulse, MAP, NTG requirement postoperatively and Level of anxiety post extubation

	Pulse	MAP	NTG requirement	Level of anxiety (n =20)			
				1	2	3	4
Baseline							
Group M	85.10±1.938	90.30±0.9655	---	0	0	50%	50%
Group N	85.00±1.606	85.50±0.7931	---	0	0	55%	45%
During extubation							
Group M	83.40±0.9958	87.50±0.8811	---			---	
Group N	96.60±1.106^{xxx}	94.20±0.8066^{xxx}	30 %			---	
15 min after extubation							
Group M	72.10±0.5889^{xxx}	83.20±0.6867^{xxx}	---	0	60%	40%	0
Group N	83.70±1.059	92.50±0.8062^{xxx}	---	0	65%	35%	0
1 hour after extubation							
Group M	71.30±0.5482^{xxx}	83.20±0.8385^{xxx}	---	85%	15%	0	0
Group N	87.30±0.9870	87.60±0.8156	---	0	100%	0	0
P value							
Group M	F = 39.35P < 0.001	F = 16.84P < 0.0001	---			---	
Group N	F = 23.03P < 0.0001	F = 25.64P < 0.0001					

(^{x} = $p < 0.05$; ^{xx} = $p < 0.001$; ^{xxx} = $P < 0.0001$, NTG = Nitroglycerine, level of anxiety : 1 = not anxious at all; 2 = somewhat; 3 = moderately so; 4 = Very much so)

DISCUSSION

We selected patients in a narrow age group of 40 to 50 years to prevent the effect of physiological changes of age on the cardiovascular system which could have brought biasness on the haemodynamic parameters. We included patients undergoing modified radical mastectomy only so as to keep uniformity in the nature of the disease, extent of surgery and the anxiety and the surgical pain associated with it as far as possible. As the stress of operation could have altered the level of anxiety and the haemodynamics on the day of surgery, we recorded the baseline anxiety level and the haemodynamics during preanaesthesia check up one week prior to surgery.

All patients anticipating surgery experiences stress and anxiety which is particularly affected by gender (higher anxiety in women), type of surgery (acute more than planned), type of anaesthesia (spinal more than general), and time before surgery (anxiety level increases with a shorter time before surgery)and this preoperational anxiety has been linked to unfavourable overall postoperative outcome of the patient.[3,13] Our finding of musical intervention resulting in decreasing the preoperative anxiety level is supported by the findings of Palmer et al.[5] In their study on 207

patients of potential or known breast cancer they have demonstrated that preoperative music therapy which is either patient selected live music or therapist selected pre recorded music, results in decrease in the preoperative anxiety scores and concluded that including music therapy as a complementary modality with cancer surgery may help manage preoperative anxiety in a way that is safe, effective, time-efficient, and enjoyable. Binns-Turner et al provided continuous music throughout the preoperative, intraoperative and postoperative period to their patients undergoing mastectomy and their findings indicated that women in the intervention group had a greater decrease in MAP and anxiety with less pain from the preoperative period to the time of discharge from the recovery room compared with women in the control group.[6] Similar observation was reported by Li et al in their randomized clinical trial on the effect of music therapy on anxiety of patients with breast cancer after radical mastectomy.[4] They studied the effect of musical intervention in reducing anxiety in the late postoperative period (on the day before patients were discharged from hospital, the second and third time of admission to hospital for chemotherapy respectively). The repeated-measure ancova model analysis indicated that the mean state anxiety score was significantly lower in the experimental group than those in the control group at each of the three post-test measurements. We observed a decrease in the anxiety level in both the groups in the postoperative period compared to the preoperative baseline scores. But this reduction in the anxiety level was more in the musical intervention group. Similar finding was published by Brenda Johnson et al whocompared the effect of music with noise blocking headphones on the level of anxiety in women undergoing gynecologic same-day surgery.[14] Both the groups experienced a drop in anxiety from pre to postoperative status, but the music group experienced the lowest postoperative anxiety scores. Bradt et al did a meticulous study of reports and publications on music interventions for preoperative anxiety.[2] They searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 7), MEDLINE (1950 to August 2012), CINAHL (1980 to August 2012), AMED (1985 to April 2011; we no longer had access to AMED after this date), EMBASE (1980 to August 2012), PsycINFO (1967 to August 2012), LILACS (1982 to August 2012), Science Citation Index (1980 to August 2012), the specialist music therapy research database (March 1 2008; database is no longer functional), CAIRSS for Music (to August 2012), Proquest Digital Dissertations (1980 to August 2012), ClinicalTrials.gov (2000 to August 2012), Current Controlled Trials (1998 to August 2012), and the National Research Register (2000 to September 2007). They hand searched music therapy journals and reference lists, and contacted relevant experts to identify unpublished manuscripts. They included all randomized and quasi-randomized trials that compared music interventions and standard care with standard care alone for reducing preoperative anxiety in surgical patients. They concluded that music interventions may provide a viable alternative to sedatives and anti-anxiety drugs for reducing preoperative anxiety. In our study also, musical intervention group displayed stable haemodynamics throughout the perioperative period, and we didn't had to use NTG for control of blood pressure in any of the cases whereas in the control group we had to use NTG in 35% of the cases to maintain the MAP, a finding which is supported by the study of Binns-Turner et al.[6] In their study, a total of 30 women undergoing mastectomy were assigned randomly to a control group or to the music intervention group. Findings indicated that women in the intervention group had a greater decrease in MAP from the preoperative period to the time of discharge from the recovery room compared with women in the control group. They concluded that perioperative music can reduce MAP among women undergoing mastectomy for breast cancer. However, Jiménez et al [15] did a controlled randomized clinical trial on safety and efficacy of music therapy on intraoperative stress and anxiety reduction and they didn't find statistical differences between the control and experimental groups in heart rate gradient or systolic and diastolic blood pressures measured after the intervention. There are not many studies on the effect of music therapy on intraoperative haemodynamics. Further studies in this aspect will be required in the near future. There is a notion that general anesthesia does not completely abolish auditory perception and that some processing of intraoperative events can occur in unconscious patients, even in the absence of postoperative recall. [16] This has been the basis for us to assume the hypothesis that intraoperative music listening can decrease anesthetic requirements and reduce isoflurane consumption. Music has been shown to reduce patient's anxiety and decrease sedative requirements.[17, 18, 19] X. W. Zhang et al evaluated the sedative effect of music using the bispectral index (BIS) during target-controlled infusion (TCI) propofol in their study on 110 women undergoing hysterectomy.[20] They were randomly allocated to receive either music or no music. The music group had a significant reduction in mean (SD) induction time of sedation: 12 (12) min vs. 18 (12) min, $p < 0.01$. Ganidagli et al assessed the effect of music on the level of sedation and the electroencephalograph bispectral index (BIS) during the preoperative period on Fifty-four ASA physical status I-II patients, scheduled for elective septo-rhinoplastic surgery and concluded that listening to music during midazolam premedication is associated with an increase in sedation level in the preoperative period as reflected by a lower BIS value.[21]In our study though we kept an upper limit of

using isoflurane to 1.2% (provided BIS was acceptable), we didn't had to increase the isoflurane concentration to more than 1 volume % in any of the cases in the music intervention group. The mean for isoflurane was 0.64 ± 0.04724 at 15 minutes after incision and 0.61 ± 0.03692 at 1 hour after incision. But in the control group the need for isoflurane was significantly higher with a mean of 0.78 ± 0.05211 at 15 minutes after incision and 0.80 ± 0.07255 at 1 hour after incision which was a statistically significant difference (p = 0.05 and 0.0250 at 15 minutes and 1 hour after incision respectively) amongst the two groups.

CONCLUSION

Music is a cheap, non pharmacological, easily available modality of therapy which can be used efficiently in the perioperative period to decrease stress and anxiety associated with surgery with additional benefit of providing stable perioperative haemodynamics and decreasing anaesthetic agent requirement in the intraoperative period.

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ORIGINAL ARTICLE

MICROBIAL COLONIZATION PROFILE OF RESPIRATORY DEVICES

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ABSTRACT

Background: The respiratory care equipment's which include nebulizers, humidifiers, and ventilators may have been identified as the potential vehicle which may cause major nosocomial infections if they are colonized by different bacteria. This study was conducted to know presence of **microbial flora in** inhalation therapy equipment, type of organisms.

Methodology: The study included 60 samples out of which 30 samples were taken from nebulizers, and 30 samples were taken from humidifier chambers in use. Rinse sampling method using 10-20 ml sterile BHI broth was performed. Quantitative culture was performed using colony counting agar spread plate method.

Result: 51.6% samples showed significant bacterial growth .Out of these 14 samples were of nebulizers and 17 samples of humidifier chambers. 90.33 % bacterial isolates were gram negative bacilli and 9.66 % were gram positive cocii. Following gram negative bacilli were isolated: Pseudomonas (41.93 %), B.cepacia (16.13%), Klebsiella species (12.9%), Acinetobacter species (12.9%) and Polymicrobial flora (6.45%).

Conclusion: Our study indicates a potential risk of nosocomial infection due to microbial colonization of various respiratory devices.

Keywords: Humidifiers Ventilators, Microbial colonization, Disinfection

INTRODUCTION

Respiratory care equipments which include humidifiers and nebulizers have been identified as potential vehicles causing major nosocomial respiratory infections if they are colonized by fungi or bacteria.[1-3] Contaminated respiratory care equipments may lead to nosocomial infections via 2 routes; firstly: Equipment may serve as a reservoir for microorganisms, especially gram-negative bacilli. The fluid containing devices such as nebulizers and humidifiers may become heavily contaminated by bacteria and fungi which may be capable of multiplying in water. The pathogens may then spread to the patients by aerosolization in the room. Secondly, the contaminated equipment may lead to a direct instillation or delivery of microorganisms to the airways, if the equipment is directly linked to a ventilator system or if contaminated medication is instilled or aerosolized. Many types of equipment such as oxygen masks and nebulizer chambers may be transferred from patient to patient several times daily but they may be seldom cleaned daily.[4-6] Autopsy material at Parkland Memorial Hospital from the years 1952, 1957, and 1963 was reviewed to determine the frequency of necrotizing pneumonia. These years were selected to represent a period before the widespread use of present inhalation therapy techniques, a period preceding the introduction of prolonged nebulization treatments, and the present period of widespread use of inhalation therapy. The frequency of gram-negative necrotizing bacillary Pneumonia in 1952 was 0.8%, in 1957 was 1.8%, but by 1963 had risen to 8.0%.The association between the increasing incidence of gram-negative necrotizing bacillary pneumonia and widespread use of inhalation therapy coupled with apparent lack of association with other predisposing factors suggested the potential role of inhalation therapy in nosocomial pulmonary infection.[7] The infection control activities should emphasize the establishment of appropriate preventive guidelines and policies and the continuing education of health care workers to maintain an optimal compliance with the preventive practices.[8, 9]

With thisin mind the study was planned with aim to determine the rate of bacterial colonization in the nebulizers, humidifier chambers in our hospital.

METHODOLOGY

All the nebulizers & humidifiers, in use in the Dept. of Medicine & Pediatrics were taken in the study (Nebulizers: 30 Humidifiers-30)

After getting permission from Institutional Ethics committee, Rinse sampling method was used for sampling nebulizer reservoirs &humidifiers.[10]

10-20 ml of sterile BHI broth was placed in the bottle or tubing, and both ends were sealed appropriately. Bottle or tubing was vigorously shaked after it was sealed, end to end approximately 50 times. Rinse fluid was decanted in a sterile container & transported immediately for bacterial culture

Culture methods for rinse fluids: Quantitative culture was performed using agar spread plate method. Two Serial 10-fold dilutions of the rinse fluid were made in sterile non bateriostatic saline. 0.1ml of each dilution was pipetted out onto a standard agar plate surface. Separate bent sterile glass spreader was used to distribute the inoculums on each surface. Plates were incubated under conditions and for periods of time sufficient to recover implicated microbial populations. Plates were examined for significant growth (more than 10^3 CFU.)

This cross sectional study was conducted from May to September 2014.

Inclusion Criteria: All the Respiratory devices (Nebulizers/Humidifiers) which were currently used in wards & ICU of Lata Mangeshkar Hospital, Digdoh were taken into the study.

Exclusion Criteria: The devices not in use were not taken into this study.

RESULTS

Thirty one out of 60 Samples showed significant bacterial growth. Out of these 14 samples were from nebulizers and 17 samples from humidifier chambers. 38.7% samples from I.C.U, 51.6% samples from Wards, 9.67% samples from OPD showed significant bacterial colonization.

Table 1: Culture Positivity in various samples

Sample site	Positive for culture (> 10^3 CFU/ml)	Negative for culture
Nebulizers	14	16
Humidifiers	17	13
Total	31	29

Out of these bacterial isolates 90.33 % were gram negative bacilli and 9.66 % were gram positive cocci. Out of 90.32% gram negative bacilli, maximum (41.93%) were Pseudomonas, 12.90% were Klebsiella, 12.9% were Acinetobacter, 16.12% were Burkholderia cepacia Polymicrobial growth (more than one organism) was seen in 6.45% samples.

Table 2: Organism isolated (n=31)

Species	Nebulizers (n=14)	Humidifiers (n=17)	Total (%)
Pseudomonas	7	6	13 (41.9)
Klebsiella	2	2	4 (12.9)
Burkholderia Cepacia	1	4	5 (16.1)
Acinetobacter	1	3	4 (12.9)
Coagulase Negative Staphylococcus	1	0	1(3.2)
Staphy aureus	1	0	1(3.2)
Poly microbial	0	2	2 (6.5)

Table 3: Split up of Polymicrobial Flora isolated

Polymicrobial-1	E.Coli+ Pseudomonas
Polymicrobial-2	Klebsiella + Staphylococcus aureus

DISCUSSION

Respiratory infections are the commonest among nosocomial infections. Nosocomial pneumonia is the second most common nosocomial infection worldwide and the most common infection in intensive care units (ICUs). In the United States, The Center for Disease Control and prevention (CDC) roughly estimated 1.7 million hospital-associated infections from all types of microorganisms which included bacteria, fungi and viruses, which contributed to 99,000 deaths per year.[11] Most nosocomial infections in hospitals worldwide are linked to some human activities near or inside the hospitals, to available water supply, contaminated air and medical devices or equipment used in the health care delivery. In this study, a Nebulisers & Humidifiers, which are commonly used respiratory devices were screened to determine rate of colonization & type of bacteria present. The presence of organisms on the medical devices highlights the flaws on the cleaning and disinfection processes of medical equipment.[12, 13, 14]

Nebulizers create aerosols of minute droplets that penetrate deeply into the narrowest airways and thus present a significant problem. This is especially so for small volume medication nebulizers.[15] In our study we studied 30 nebulizers which were in use in various sections of our hospital. Fifteen samples were taken from nebulizers in I.C.U, 7 samples were taken from wards, 8 samples were taken from OPD Nebulizers. Out of these thirty nebulizers we found a significant growth of bacteria in fourteen nebulizers. Nebulizers used to deliver medication easily become contaminated. They should be washed with detergent and dried every time they are used. Mouthpieces should be Changed every 24 hours.[16] Humidifiers: Humidification of the circuit is essential to prevent dehydration of the airways. Humidifiers do not produce aerosols so if the water in the reservoir becomes contaminated, the bacteria are less likely to be inhaled. However, water vapor tends to condense in

the tubing. The condensate may become heavily contaminated and can drain into the trachea, increasing the risk of infection. Humidifiers should be filled with sterile water and decontaminated every 48 hours.[11] In the present study 30 humidifiers were studied which were in use in various sections of hospital out of which 17 samples were taken from humidifiers in I.C.U, 13 samples were taken from humidifiers in wards,. Out of these significant growth of bacteria was seen in 17 humidifiers. In Present study the positivity rate for bacterial colonization in nebulizers and humidifiers was 50% and 56.66% respectively. Similar study was carried out by Savita Jadhav et al, in her study the positivity rate for bacterial colonization in nebulizers and humidifiers was 47.5% & 78.26% respectively.[17]

We found that predominantly gram negative organisms were present in nebulizers and humidifiers (90.33 %). Similar studies have showed varying degree of colonisation but with preponderence of gram negative bacteria. Study by Savita Jadhav et al [17] showed 68.85% gram negative bacteria & 31.14% gram positive bacteria The most common organism in present study was Pseudomonas aeruginousa, 13(41.93%)& B.cepacia, 5 (16.12%) followed by Klebsiella, 4 (12.90%)(Table-2) Most common bacterial isolate in the study of Savita Jadhav et al was Pseudomonas (39.53%) followed by Acinetobacter (13.9%) and Klebsiella(9.52%). Both the studies indicate approximately similar bacterial isolation, with predominance of Pseudomonas species. Although studies of infectivity of aerosols have shown that inhalation therapy equipment frequently generates significant bacterial aerosols but we need to evaluate the potential pathogenecity of these aerosols which are dependent on various factors like Particle size of aerosols & Minimum infectious dose

CONCLUSION

Our study indicates a potential risk of nosocomial infection due to microbial colonization of various respiratory devices. The nebulizers and humidifier chambers need to be cleaned more frequently with disinfectants, to control nosocomial infections. Proper cleaning and sterilization or a high level disinfection of the reusable equipment is essential, to prevent the infections which are associated with the respiratory therapies such as oxygen therapy, nebulization, etc. Devices or parts of devices need to be rinsed with water after they have been chemically disinfected. The implementation of new and regular hygiene measures for the maintenance of such equipments is desirable.

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ORIGINAL ARTICLE

PROFILE OF CONGENITAL SURGICAL ANOMALIES IN NEONATES ADMITTED TO TERTIARY CARE NEONATAL INTENSIVE CARE UNIT OF SAURASHTRA REGION

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ABSTRACT

Background: Congenital surgical anomaly is a major indication for admission of a neonate to an intensive care unit. Profile of surgical conditions is variable by system affecting the neonate and outcomes of the individual conditions depending upon treatment and post surgical facilities. This study was undertaken to highlight the surgical conditions, their burden and their prognosis encountered in our newborn care unit.

Methodology: This study is a cross sectional study. All information was collected from the case records of all neonates admitted in newborn care unit of our centre between 1st April, 2011 and 31st October, 2014 with congenital surgical conditions and the following information extracted: surgical condition, age, sex, maturity, birth weight, its treatment and outcome, and other associated features were studied.

Result: A total of 9213 neonates were admitted in the study period, of which 328 neonates (3.6%) had surgical conditions. Surgery was performed in 225 neonates. Commonest congenital surgical condition was of gastrointestinal tract (GIT). Commonest GIT anomalies were tracheo-oesophageal fistula (28.6%), intestinal obstruction (23.7%), anorectal malformation (17.9%), and omphalocoele (7%). The overall mortality in neonates with congenital surgical condition in this study was 51.2%. Significantly, more deaths occurred in preterm than in term neonates (P = 0.00003) and low birth weight babies more than normal weight (p=0.0002).

Conclusion: High mortality is found in neonates suffering from surgical conditions. Commonest anomaly includes conditions of Gastrointestinal tract. Prematurity and low birth weight is a significant factor associated with high mortality.

Keywords: Neonate, surgical anomalies, congenital

INTRODUCTION

Neonatal surgical conditions are important causes for neonatal mortality and morbidities. Outcome and burden is variable from disease to disease and facility to facility. Surgical neonates are a subclass of patients having wide differences in physiology, anatomy, diseases, immunity and response to the stress, as compared to older patients.

Though paediatric and neonatal surgery has made great strides globally in many centres, including ours, the surgical emergencies are first diagnosed by the neonatologists and paediatricians. Not only the neonatologists make the preliminary diagnoses but also help in stabilizing these neonates for a successful surgical intervention. In a developing country like ours, resource crunch in regard to manpower, money and machines dictates avoiding duplication of services within the same hospital. No wonder the neonatologists have often even offered to manage the patients post operatively. There is a better outcome in surgical neonates when they are in safe hands of expert paediatric surgeon and neonatal intestivist.

In developed countries, outcome of neonatal surgical cases is favourable because of availability of antenatal diagnosis, improved surgical skills and technologies, sophisticated neonatal intensive care unit, availability of total parenteral nutrition and adequate staff. In developing countries, however, neonatal surgery is still fraught with a lot of problems including late presentation and lack of medical facilities and human resources, thereby, making newborn surgery to be associated with unacceptably high morbidity and mortality.

The aim of this study was to provide information on clinical profile of congenital surgical problems and to highlight their burden and prognosis in our new born intensive care unit in Saurashtra region.

METHODOLOGY

This is a cross sectional study, in which a retrospective analysis of all case records of neonates with a surgical problem admitted to level III NICU of a tertiary health care referral centre between1st April, 2011 and 31st October, 2014 was studied. Institutional ethical committee clearance was obtained before starting the study. Patients with any acquired form of surgical conditions (like abscess, NEC) were excluded from the study.

Surgical cases are handled by paediatric surgeons and paediatrician. Case notes and admission records in newborn unit were used to extract the following information: Sex, age at presentation, date of admission, maturity, surgical condition, treatment and prognosis (outcome of the management). Data was entered in an Excel spread sheet and analysed using Epi Info version 3.5.1. Categorical data were analysed using the Chi-square test and a *P*-value $\leq$0.05 was regarded as significant.

RESULTS

A total of 9213 neonates were admitted within the study. 328 (3.6%) had surgical condition. General characteristics of these neonates are shown in Table 1.

Table 1: General characteristics of the neonates with surgical conditions

Variables	Admitted No. (%)
Total admission	9213
Neonates with surgical conditions	328(3.6)
Male	196(59.8)
Female	132(40.2)
Death	168(51.2)
Intramural	53(16.2)
Extramural	275 (83.8)
Low birthweight	185(56.4)
Normal birth weight	143(43.6)
Preterm	130 (65.6)
Term	198 (60.4)

Out of these 196 (59.8%) were males and 132 (40.2%) were females. Average age on admission was 5days (Range 1 day to 30 days). The average birth weight was 2.4 kg (Range 1.1kg to 4.0kg). Out of 185 neonates with low birth weight with surgical conditions 111(60.1%) died which was statistically significant (P =0.00003). Out of 130 premature neonates 85(65.3%) died which was statistically significant (P = 0.0002).

Following table-2 shows neonates which presented with the following surgical conditions and their outcome.

TABLE 2: Neonates with surgical conditions and outcome

System Involved	Surgical Condition	Admission (N=328)	Survival (%)	Expired (%)	Dama (%)	Refer (%)
Lower GI System	Intestinal Obstruction	78	35(44.8)	31(39.7)	9(11.5)	3(3.84)
	Imperforate Anus	63	32(50.7)	22(34.9)	8(12.7)	1(1.6)
	Inguinal Hernia	2	1(50)	-	1(500	-
	Intestinal Malformation	1	-	1(100)	-	-
	Microcolon	1	1(100)	-	-	-
	Total	**145**	**69(47.6)**	**54(37.2)**	**18(12.4)**	**4(2.8)**
Upper GI System	Tracheosophageal Fistula	94	9(9.6)	67(71.2)	12(12.7)	6(6.3)
	Atresia Of Upper Gi Tract	14	2(14.2)	10(71.4)	2(14.2)	-
	Diaphragmatic Hernia	17	1(5.9)	15(88.2)	-	1(5.9)
	Pyloric Stenosis	3	-	-	3(100)	-
	Total	**128**	**12(9.3)**	**92(71.8)**	**17(13.2)**	**7(5.4)**
Anterier Abdominal Wall Defect	Omphalocele	23	2(8.7)	12(52.1)	7(30.4)	2(8.7)
	Gastrochiasis	6	-	4(66.6)	2(33.3)	-
	Umbilical Hernia	5	2(40)	2(40)	1(20)	-
	Extrophy Of Bladder	1	1(100)	-	-	-
	Total	**35**	**5(14.2)**	**18(51.4)**	**10(28.5)**	**2(5.7)**
CNS System	Hydrocephalus	7	-	3(42.8)	2(28.6)	2(28.6)
	Spina Bifida	5	-	-	1(20)	4(80)
	Meningomyelocele	3	-	-	1(33.3)	2(66.6)
	Total	**15**	**-**	**3(20)**	**4(26.6)**	**8(53.3)**
Genito Urinary System	Hypospadias	3	-	-	3(100)	-
	Posterier Urethral Valve	1	-	-	-	1(100)
	Scrotal Teratoma	1	-	1(100)	-	-
	Total	**5**	**-**	**1(20)**	**3(60)**	**1(20)**

(DAMA discharged against medical advice)

The most common system involved in neonates presenting with congenital surgical conditions was gastrointestinal tract(GIT).Commonest GIT anomalies were tracheo-oesophageal fistula (28.6%), intestinal obstruction (23.7%), anorectal malformation (17.9%), and omphalocoele (7%). The commonest surgical interventions were laparotomy, intestinal resection and anastomosis, colostomy and closure of abdominal wall defect.

Table 3 shows management and outcome of all neonates admitted with surgical condition.

The table-2 above shows better outcome with patients with lower GIT involvement in patients having anorectal malformation followed by intestinal obstruction. Poor outcome and expiry seen in neonates with intestinal malformation, diaphragmatic hernia, tracheo-oesophageal fistula, GI atresia, gastrochiasis. It was observed that major surgeries involving laparotomy and lengthy and complex procedures had poor outcome.

Table 3:. Management and outcome of neonatal surgical cases

Intervention	No (%)	Male (%)	Female (%)	Discharge (%)	Died (%)	Dama (%)	Refer (%)
Surgery performed	225 (68.5)	127 (56.4)	98(43.6)	86(38.2)	131(58.2)	7(3.1)	1(3.1)
No surgery	103(31.4)	69(67.0)	34(33.0)	0	37(35.9)	45(43.7)	21(20.4)
Total	328	196	132	86	168	52	22

DISCUSSION AND CONCLUSION

In our study 3.6% of the NICU admissions were due to neonatal surgical conditions. It was higher than 3.0% reported in a study by Shija JK in Tanzania.[1], however, the study was over 3and1/2 year period as against the present study that was over an 8-year period In a study by Ugwu RO in Nigeria, this incidence was 6.2%.[2]

The most common surgical conditions in the newborn involve the gastrointestinal tract. [3]In our study GIT anomalies were (56.9%), whereas in the study by Ugwu RO in Nigeria (43.7%).[2]

The mortality in neonates with surgical condition in this study was 51.2%. Other authors had earlier reported lower mortalities ranging from 30.5% to 42.3%.[4,5,6,7] A higher mortality of 53.6% is reported in another study.[8]

Significantly, more deaths occurred in preterm babies and low birth babies. Mortality generally is known to be higher in preterm babies because of the immaturity of all physiologic functions and other multiple confounding factors.

Major limitation of our study was that it was a retrospective case based study, and not all the detailed information pertaining to cases could be extracted from the records.

Lower GI anomalies are common making a major part of congenital surgical anomalies in neonates, followed by upper GI anomalies. Survival of neonates having surgical anomalies varies according to profile of anomalies with better outcomes in the patients of lower GI tract anomalies. Prematurity and low birth weight are important risk factors for poor outcomes in neonates with surgical anomalies.

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ORIGINAL ARTICLE

A CLINICAL STUDY ON EAR TRAUMA IN SOUTH INDIA

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ABSTRACT

Aim: To review about the presentations, types and aetiology of factors affecting ear trauma in patients of Konaseema region of Andhra Pradesh in South India and recommend appropriate management.

Materials and Methods: All patients treated for ear trauma at Konaseema Institute of Medical Sciences & Research Foundation of Andhra Pradesh in South India for a period of one year from 1st January 2015 to 31st December 2015 were studied using their clinical records after obtaining ethical committee clearence. Data extracted were analysed by using SPSS software.

Results: The results were presented in simple descriptive and tabular forms. Total 43 patients, out of which, 37(84%) males and 6(16%) females, of ages 10 to 70 years, average age of 33.41 years were studied. Road traffic accidents RTA 35(81.39%) was the commonest aetiology while bleeding from the ear 26(60.46%), tympanic membrane perforation 25 (58.13%), Ear laceration 12(27.90%) and ear contusion haematomas 5(11.62%) were other frequent presentations.

Discussion: In ear trauma tympanic membrane is mostly affected. Sudden increase in canal pressure from trauma by Road traffic accidents or blows/slaps were the major mechanism of injury.

Conclusion: Early Management of all ear trauma cases was good except for few late presenters with complications.

Keywords: Ear, RTA, Trauma, Aetiology, Presentation

INTRODUCTION

Ear trauma is a reflection of increasing number of road and other accidents, physical assaults, contact sports and other forms of trauma. The external, middle and inner ear may be affected in isolation or together depending on the force and agent of trauma. The lesions may range from simple blunt trauma to the pinna, without loss of tissue, through uncomplicated rupture of the tympanic membrane to transverse fracture of the petrous temporal bone with complete loss of inner ear and facial nerve function. Outside the nose the auricle occupies the most prominent position in the face. Its exposed and unprotected position makes it susceptible to injuries. Lesions encountered include swelling or haematoma[1,2] Lacerations[3] abrasions or even complete avulsion. Middle ear injury frequently results from direct trauma through the external auditory canal or Penetrating trauma. Regardless of the mechanism of injury the tympanic membrane is typically perforated resulting in a conductive hearing loss. Damage to the ossicles, facial nerve and inner ear structures may result from severe trauma. Temporal bone fractures may equally lead to such damage. In this paper, we present a retrospective study of presentation, type and aetiology of ear trauma cases seen at Konaseema Institute of Medical Sciences and Research Foundation, Amalapuram in Andhra Pradesh of South India, over a period of one year. The outcome will enable us to establish the pattern of ear trauma in the sub-region.

METHODS

All patients treated for any cause of ear trauma from Jan 2015–December 2015 in Konaseema Institute of Medical Sciences and Research Foundation, Amalapuram in Andhra Pradesh of South India were studied retrospectively from their clinical records which were certified to contain clear details of the trauma and management offered after obtaining clearance of ethical committee of the institute. Their bio-data and other relevant information were also extracted. The data obtained were analysed using SPSS software and results presented in simple descriptive and tabular forms.

RESULTS

In our study out of 43 patients, 37(84%) were males and 6(16%) were females of ratio accounting to 6.16: 1. Their ages ranged from 10 to 70 years with average age of 33.41 years. Young people were more involved with 21–30 years being the modal age-group affected Table 1. The aetiologies noted were predominated by road traffic accidents RTA 35(81.39%) Table 2. The left ear 23(53.48%) compared to the right ear 15(34.88%) was mostly affected and in 5(11.62%)cases both ears were involved. Acute presentation with bleeding from the ear 26(60.46%) topped the list of presenting signs and symptoms, Table 3.

Young people were more involved with 21–30years being the modal age-group affected. The aetiologies noted were predominated by road traffic accidents RTA 35(81.39%). Acute presentation with bleeding from the ear 26(60.46%) topped the list of presenting signs and symptoms.

Table 1: Patient's Age (n=43)

Age group	No. (%)
1-10	1(2.32)
11-20	7(16.27)
21-30	14(32.55)
31-40	9(20.93)
41-50	5(11.62)
51-60	6(13.00)
61-70	1(2.00)

Table 2: Cause of Ear Trauma (n=43)

Etiology	No. (%)
RTA	35(81.39)
Assault	2(4.65)
Fall	5(11.62)
Cause not known	1(2.32)

Table 3: Presentations

Sign/Symptom	No. (%)
Bleeding from ear	26(60.46)
Tympanic membrane perforation	25(58.13)
Deafness	25(58.13)
Abrasion	23(53.48)
Tinnitus	22(51.6)
Lacerations	12(27.90)
Otto rhea	5(11.62)
Hematoma	5(11.62)
Cauliflower ear	1(2.32)

DISCUSSION

Ear trauma in this study occurred mostly to young males. This is the age group that is engaged in many activities like Sports, Fights, Bike races etc. In our study Road traffic accidents was common cause of ear injury. The sheering force mostly in RTA resulted in Abrasions and Lacerations. Blunt Trauma due to hitting ground resulted in ear bleeding, Tympanic Membrane perforation and haematoma.

Literature reveals right and left sided injuries were equally common. In our study, left sided injury 23(53.48%) dominated with right side injury 15(34.48 %) and involvement of both ears is 5(11.62%). Abrasion 23(53.48%), laceration 12 (27.90%) and haematoma 5 (11.62%) were the presentations referable to the external ear. Abrasions were the commonest form of accidental ear injury 23(53.48%) in our study. Lesions affecting the pinna can lead to disfigurement and change the appeal of the face; they require appropriate intervention. The aim of treatment should be to restore the normal contours of the ear and prevent infection. Prompt surgical intervention with extra cartilaginous suturing under good antibiotic cover as applied in our patients achieved this [1,2,3,4]. Pressure dressing following surgical drainage helped to avoid re-accumulation in case of haematoma. The location of the haematoma within the cartilage itself has been postulated as one of the primary reasons for initial failure [4]. One of the five haematoma cases developed cauliflower ears before presenting. This was as a result of late presentation and the outcome was not as good as the early presenters. Majority of the patients came with bleeding from the ear 26 (60.46%), and perforation of the tympanic membrane 25 (58.13%) associated with temporary hearing loss in 25 (58.13%) and tinnitus in 22 (51.16%) cases implicating the force and severity of injury sustained. Bleeding could be in the external auditory canal, associated with tympanic membrane perforation or deeper middle ear structures or fracture to base of skull/temporal bone. Early presentation and evaluation helps to resolve the issue by appropriate intervention. Traumatic perforations of the TM are often encountered in the emergency room and primary care setting [5] resulted from RTA, and domestic fights/brawls.

There are various causes of acute traumatic rupture of the tympanic membrane that have been reported [6–14]. Open-hand blows, injuries by cotton tipped swabs or foreign bodies, explosions, welding sparks, fracture injury to the temporal bone, barometric causes due to pressure changes like flying, iatrogenic causes such as vigorous syringing of the ear or surgical intervention during insertion of ventilating tubes have been listed [6,8,9]. The trauma causes a sudden increase in the ear canal air pressure [14] leading to rupture of TM. The ear is the organ that is most vulnerable to damage by blast pressure [15,16]. An increase in pressure as little as 5 psi above atmospheric pressure (1atm is equivalent to 14.7 psi, or 760 mm Hg) can rupture the ear drum [17]. The tendency to rupture increases with age with atrophic segments likely to rupture at pressure changes at least 50% lower than a

normal tympanic membrane [17]. In our study there was no case of blast over pressure or explosions. Road traffic accidents (RTA) were the most frequent aetiology in our study. Most of the injuries sustained were of mild to moderate severity and limited to external and middle ears .Baseline pure tone audiometry's were done on presentation, showed mild to moderate hearing loss. Average decibel loss in such people were noted to be <30 dB. Most of the audiograms were obtained within 24 h to 4 days of presentation to the emergency department or clinic. TM perforation closure by healing resulted in 10–20 dB improvement of air-conduction threshold. Majority of these patients returned to normal or near normal hearing. Though controversies exist on the best method of treating traumatic perforations of the tympanic membrane; it has been shown that most acute traumatic perforations heal spontaneously [6, 7, 11, 18, 19]. In our study, the TM healed spontaneously with prophylactic antibiotic coverage and strict following of instruction not to allow water or any other fluid to enter the ear. By 1–2 months of follow up there was complete healing of the TM and return to normal hearing in majority of uncomplicated cases.

Amadasun [20] prospectively examined, in three sections, a group of patients with a cellophane patch (n = 6), another group with a gentamicin ointment seal (n = 15) and a control group (n = 9) with a gentamicin plug placed at the distal end of the external auditory cavity. He achieved successful healing of the traumatic tympanic membrane perforations in 50% of the cellophane seal group, 86.7% of the gentamicin ointment seal group and 77.8% of the control group. He concluded that the management of a fresh tympanic membrane perforation should be clean to prevent infection. Other studies have showed no difference between paper prosthesis and spontaneous healing with treatment by oral antibiotics [18, 19, 21]. However, the mechanism of injury and size of perforation influence the rate of spontaneous healing [19]. The aims of treatment in middle ear injury are to achieve an intact tympanic membrane and restoration of hearing. These are achieved with early presentation and appropriate management. Late presentation and wrong intervention predispose to complications with poor outcome. This was validated in our study by otorrhoea in 5(11.62%) cases and cauliflower ear in 1(2.32%) case. This is due to improper interventions and, delay in presentation as well as ignorance. It was due to the complications that the patients presented for proper treatment.

CONCLUSIONS

We recommend early intervention, wound debridement, early repair, good antibiotic coverage in ear trauma can yield better out come and good cosmetic results with least complications.

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ORIGINAL ARTICLE

A STUDY ON COMPARISON OF OPEN REDUCTION INTERNAL PLATE FIXATION (ORIF) AND MINIMALLY INVASIVE PERCUTANEOUS PLATE OSTEOSYNTHESIS (MIPPO) TECHNIQUE ON SCHATZKER IV-VI TIBIAL PLATAEU FRACTURES

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ABSTRACT

Background: Tibial condyle fractures in young adults or in old age are difficult to manage conservatively and often require operative management. The present study was conducted with an objective to compare the results of Open Reduction Internal Plate Fixation (ORIF) Technique and Minimally Invasive Percutaneous Plate Osteosynthesis (MIPPO) technique for S**chatzker** IV-VI tibial plateau fractures.

Methods: The case records of 42 cases of schatzker IV-VI type tibial fracture were analyzed retrospectively. Among these 42 patients 21 received surgical treatments in the form of ORIF with plate fixation and other 21 cases received MIPPO after 7-10 days after injury. The surgical time, complication, length of hospital stay and cost of hospitalization were analyzed and compared between two groups.

Results: There was no significant differences in time required for operation between 2 groups ($p>0.05$) while there was significant differences observed ($p<0.01$) for duration of stay in hospital and cost of hospital stay. After 9-24 months follow up (average12 months), no difference was found between two groups in terms of complication, healing time or hospital for special surgery score (HSS). No deep infection was found in both groups however superficial infection was found in 5 patients in group 2.

Conclusion: It is concluded from the present study that under certain conditions MIPPO for complex tibial plateau fractures is feasible as it can shorten the length of stay, decrease cost of hospitalization and promote early functional rehabilitation.

Keywords: Tibial Fractures, SCHATZKER Classification, Minimally Invasive Percutaneous Plate Osteosynthesis (MIPPO), Open Reduction Internal Fixation (ORIF)

INTRODUCTION

Tibial condyle fractures which are many times due to high energy trauma in young adults or trivial trauma in old age are difficult to manage conservatively only and often operative management is required. Operative management is usually internal fixation with plates (T or L buttress plates or locking plates) reduction of fractures accurate or rigid fixation.[1] Early mobilization is the key for getting good results. Open reduction and internal fixation gives good results provided major complications like compartment syndrome, soft tissue envelope damage, infection, knee instability or stiffness can be avoided.[2] Often above knee slab or temporary knee spanning fixator is required to allow soft tissue condition to improve.[3]

Purpose of our study was to evaluate the overall outcome by adopting MIPPO technique in a single installation and to find whether it is better than open technique of fixation for schatzker type IV-VI fractures of tibial condyle.

METHODOLOGY

The present study was a retrospective review of all type IV V VI proximal tibial fractures operated at our institution from April 2005 to April 2015. We collected the data of patients from the hospital records. We excluded the patients who had open fractures, pathological fractures, pediatric & extra articular fractures of proximal tibia & those with neurovascular injury. Preoperative condition, X-rays operative notes postoperative complications, clinical &

functional outcome over period of 3 months & 12 months post surgery were collected for all the cases. Fractures were classified according to schatzker classification system. Most of the patients in the study were operated about 7-10 days after trauma.

Patients in group 1 were operated by Minimally Invasive Percutaneous Plate Osteosynthesis (MIPPO) technique while those in group 2 were operated by Open Reduction and Internal Fixation (ORIF) with plates (T or L buttress) single approach. While 1 incision was done for type IV and double approach via lateral and medial incision was for type V & VI fractures in MIPPO technique. In group 2 type V & VI fractures, one incision was done for both lateral and medial platting. Post operative patients were give antibiotics, analgesics. Physiotherapy with unloaded walking with crutches was given, weight loading after union was allowed.

Statistical Analysis: The data was analyzed using epi-info software. Measurement of continuous variable was expressed as mean ± Standard deviation. The continous variables were compared using student's T test. Dichotomous variable were compared using chi-square test and statistical significance was noted at $p<0.05$.

RESULTS

There were 42 cases included in this study. Gender distribution shows that there were 30 males and 12 females. There were 21 cases each in Group 1 (MIPPO) and Group 2 (ORIP). The demographic distribution of cases was as shown in table 1. There was no significant association between the groups with age and gender distribution of cases ($p>0.05$). Distribution of SCHATZKER comparison of fracture type between 2 groups was as seen.

Average follow up duration was 12 months ranging from 9 months to 2 yrs. Neither nonunion nor deep infection was found in 2 groups. At early period (3 months) after operation, HSS score was found to be significantly different between 2 groups ($p>0.05$) (table 3).

There were no complications seen intra operatively among the cases. No deep infection was found in both groups however superficial infection was found in 5 patients in group 2 which were treated by giving i.v. antibiotics. There was no significant differences in time required for operation between 2 groups ($p>0.05$) (Table 4). There was significant differences observed between 2 groups ($p<0.01$) for duration of stay in hospital and cost of hospital stay. (Table 4) After 9-24 months follow up (average12 months), no difference was found between two groups in terms of complication, healing time or hospital for special surgery score (HSS).

Table 1: Demographic distribution of cases (n=42)

Group	Age yrs (mean ± SD)	Gender	
		Male	Female
Group 1 **(n=21)**	45.33±11.24	16 (76.2)	5 (23.8)
Group 2 **(n=21)**	45.76±11.72	14 (66.7)	7 (33.3)
P value	0.904	0.495	

Table 2: SCHATZKER comparison of fracture type between 2 groups

Group	Type IV	Type V	Type VI
Group 1 (n=21)	7 (33.3)	9 (42.9)	5 (23.8)
Group 2 (n=21)	4 (19)	10 (47.6)	7 (33.3)

P value 0.548

Table 3: Comparison of the results of follow up between groups

Groups	HSS score post op	
	(3 months)	(12 months)
Group 1 MIPPO	68.33 ± 7.65	86.111 ± 7.05
Group 2 ORIF	62.71 ± 6.44	85.63 ± 5.93
P value	0.014	0.824

Table 4: Comparison of operation time, hospital stay, hospital cost

Groups	Operating time	Hospital stay	Hospital cost (Rs 10,000)
Group 1	116.3 ± 12.01	7.43±2.04	28.015±2.587
Group 2	121.76±-11.89	14.76±1.84	30.744±3.444
P value	0.149	0.64	0.006

DISCUSSION

Tibial condyl fractures schatzker type IV-VI generally managed by operative technique of platting (T OR L buttress 4.5 mm plates of locking compression plates). Conventional open reduction and internal fixation has been considered as gold standard for management but complications like compartment syndrome, soft tissue envelope damage, infections, knee instability or stiffness are well known. In the present study, we found out that through major complications like deep infection or compartment syndrome were not seen in our study patients who were operated by open techniques there was significant differences in function as evaluated by HSS score at 3 months. However this difference is not significant at 1 year of follow up. In comparison with conventional plate fixation technique, in MIPPO incision & operative exposure is small and thus less soft tissue envelope damage leading to early bone healing and less joint stiffness in HSS at 3 months. Also it has been shown that MIPPO greatly shorten hospitalization time and cost.

During open reduction, the fracture site is not always easily approached because of the open wound and the need to avoid further damage to already injured

soft tissues. Moreover, disturbance of blood supply to the fracture site cannot be avoided, and thus, non-union and infection occur with high incidence. In the present study 11.9% cases had superficial infection. Most authors have reporting rates of 18% or more for deep infection. [4,5]

As a result of the problems associated with open reduction and plating described above, recent studies have addressed the use of external fixators,[6,14,15)] but although the incidence of infection is clearly better than that of plating, it is not always easy to reduce and adequately maintain fractures, especially fractures with articular involvement or comminuted proximal tibial fractures. Furthermore, mal-union, joint motion limitations, and patient inconvenience are main concerns when an external fixator is used, and pin tract infections remain problematic.

Finally we underline that this study is retrospective analysis & number of cases is small and so the results may need further verification.

CONCLUSION

It is concluded from the present study that under certain conditions MIPPO for complex tibial plateau fractures is feasible as it can shorten the length of stay, decrease cost of hospitalization and promote early functional rehabilitation.

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ORIGINAL ARTICLE

CLINICAL PROFILE OF PATIENTS WITH CONGENITAL ADRENAL HYPERPLASIA DUE TO 21 HYDROXYLASE DEFIICIENCY

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ABSTRACT

Introduction: 21 Hydroxylase deficiency is the most common enzymatic deficiency seen in XX-DSDs. 11-deoxycorticosterone and 11-deoxycortisol are deficient in the most-severe, "salt-wasting" form of this disease. This study aimed to see clinical profile of CAH patients in a tertiary care hospital.

Methodology: This study was carried over a period of 36 months. All patients who presented to hospital with features suggestive of congenital adrenal hyperplasia were examined thoroughly. These patients were evaluated for possibility of congenital adrenal hyperplasia after their initial resuscitation and stabilization.

Results: Over a period of 36 months, 40 patients with congenital adrenal hyperplasia were diagnosed. We diagnosed 32 cases as salt losing CAH. Median age of presentation was 36 days with range from 1- 90 days. 20 patients presented with recurrent vomiting, refusal of feeds, lethargy and dehydration. 23 of 32 patients presented in shock. 16 patients were products of consanguineous marriage. 26 cases had hyponatremia (<135mg/litre) at presentation. 17 patients had hyperkalemia (serum potassium>5.5mg/litre) at admission. 7 cases had hypoglycemia at presentation. 6 patients were diagnosed as having simple virilizing CAH. One patient presented at 5 years of age with precocious puberty and another presented during evaluation of undescended testis at age of four and a half years.

Conclusion: Congenital adrenal hyperplasia is a unique disorder due to very adverse outcomes and even death resulting from enzyme deficiency if left untreated; and associated social taboos There is a need to start neonatal screening for CAH in our country.

Keywords: Congenital adrenal hyperplasia, clinical profile, screening

INTRODUCTION

On a world-wide scale, XX-Disorders of Sexual Development is the commonest of type of Disorders of Sexual Development (DSD), forming 75% of DSDs, and is seen in all populations and race groups[1]. It is a result of an enzymatic deficiency in the cortisone / 11-deoxycorticosterone biosynthesis[2]. This deficiency gives rise to a build-up of precursors, which leads to a phenotypic androgenization. 21 Hydroxylase deficiency is the most common enzymatic deficiency seen in XX-DSDs[3]. This P450 enzyme (CYP21, P450c21) hydroxylates progesterone and 17-hydroxyprogesterone to yield 11-deoxycorticosterone and 11-deoxycortisol, respectively. These conversions are required for synthesis of aldosterone and cortisol, respectively. Both hormones are deficient in the most-severe, "salt-wasting" form of the disease. Slightly less-severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin; this is termed "simple virilizing disease". These 2 forms are collectively termed classic 21-hydroxylase deficiency. Patients with nonclassic disease have relatively mildly elevated levels of androgens and may be asymptomatic or have signs of androgen excess at any time after birth[3]. Clinical presentation is dependent, in part, on the genotype.

The objective of this study was to determine the clinical profile of patients with CAH (congenital adrenal hyperplasia) in a tertiary care hospital.

METHODOLOGY

This study was carried over a period of 36 months in the Pediatrics department of a tertiary care hospital

in North India. This study was approved by the institutional ethics committee. All patients who presented to hospital with features suggestive of congenital adrenal hyperplasia, viz dehydration, shock, electrolyte imbalances, failure to thrive, ambiguous genitalia, recurrent vomiting or genital hyperpigmentation were examined thoroughly. These patients were evaluated for possibility of congenital adrenal hyperplasia after their initial resuscitation and stabilization, as was demanded by their clinical condition. A written informed consent was sought from the parents of these children for inclusion in the study.

A family history of a sib death due to any similar illness as well occurrence of a similar clinical scenario in any other sib was enquired about. A history of consanguinity was also enquired about. Sex of the patients was determined on the basis of clinical examination and on basis of karyotyping when there was some genital ambiguity as per the Prader staging[4,5]. The diagnosis of Congenital adrenal hyperplasia was made as per the Endocrine Society guidelines.[6]

RESULTS

Over a period of 36 months, 40 patients with congenital adrenal hyperplasia were diagnosed in this study.

We diagnosed 32 cases as salt losing CAH. Median age of presentation was 36 days with range from 1-90 days (**Table 1**). 20 patients presented with recurrent vomiting, refusal of feeds, lethargy and dehydration. 6 presented with only complaints of lethargy and refusal of feeds. 4 patients presented during routine neonatal examination with ambiguous genitalia and two presented with a history unexplained sib deaths (**Table 2**).

6 of these patients had a family history of sib death. 23 of 32 patients presented in shock. 16 patients were products of consanguineous marriage. All patients were born at term with a mean birth weight of 3.04kg (range 2.3 - 4kg). Presentation weight of 13 patients was less than birth weight. 19 patients had suboptimal weight gain, below the expected norms. Mean phallus length in these patients was 1.86cm (range 1.5- 2.4cm) and mean phallus width was 0.9 cm (range 0.8-1.1cm). 24 of 32 cases had metabolic acidosis at presentation. 26 cases had hyponatremia (<135mg/litre) at presentation. 17 patients had hyperkalemia (serum potassium>5.5mg/litre) at admission. 7 cases had hypoglycemia at presentation, with a blood glucose level of less than 40mg/dl **(Table 3).**

Only one patient had adrenal hyperplasia on USG. Rest of the patients had a normal ultrasound scan.13 cases had ambiguous genitalia and karyotyping proved all of them to be females. 9 patients were phenotypically females and 10 were phenotypically males. All patients had 17-hydroxyprogesterone levels more than 20ng/ml. Out of 32 cases 28 had testosterone levels greater than pre-pubertal levels. 25 patients had serum cortisol levels<1 microgram/dl. Only one patient had low LH levels. Rest of the 31 patients had normal LH levels. Only one patient had a low FSH level. Rest of them had normal FSH levels.

Table 1: Baseline characters of Salt Losing CAH Patients

Characteristics	Measure (Range)
Median Age at presentation	36 days (1-90days)
Term vs Preterm Delivery	32:0
Consanguinity Vs Non-Consanguinity	16:16
Mean birth weight	3.04Kg (2.3-4Kg)
Mean Phallus Length	1.86cm (1.5-2.4cm)
Mean Phallus Width	0.9cm(0.8-1.1cm)

Table 2: Presenting Complaints of Salt Losing CAH Patients

Presenting Complaints	No. (%)
Shock	23(71.87)
Recurrent Vomiting, Refusal of feeds, lethargy & dehydration	20 (62.5)
Lethargy & refusal of feeds	6(18.75)
Ambiguous genitalia	4(12.5)
Unexplained sib deaths	2(6.25)

Table 3: Biochemical abnormalities in Salt Losing CAH Patients at presentation

Biochemical Abnormality	No. (%)
Metabolic acidosis	24(75.0)
Hyponatremia	26(81.25)
Hyperkalemia	17(53.12)
Hypoglycemia	7(21.87)

Table 4: Baseline characters of Simple Virilizing CAH Patients

Characteristics	Measure(Range)
Median Age at presentation	2 days (1day-5years)
Consanguinity Vs Non-Consanguinity	3:3
History of sib death Vs no history of sib death	1:5

6 patients were diagnosed as having simple virilizing CAH. The median age of presentation in these patients was 2 days (**Table 4**). These patients presented on routine neonatal examination- one on day 1st, 3 on 2nd day and 2 on 3rd day of life. One patient presented at 5 years of age with precocious puberty and another presented during evaluation of undescended testis at age of four and a half years. 3 of them were

products of consanguineous marriage and one had a history of sib death. None of them presented with shock. Anthropometry of 5 years old patient showed weight between 1 to 2SD above mean and height between 2 to 3SD above mean. Similarly anthropometry of four and a half years old patient was showing weight at 50th centile and height between 2 to 3SD above mean. All of them had normal electrolytes blood sugar and creatinine on presentation. All of them had raised 17 hydroxy progesterone levels. Three of them had testosterone levels above normal. All of them had normal cortisol, FSH and LH levels.

DISCUSSION

Congenital adrenal hyperplasia is a very unique distressing medical condition. Not only does this condition cause the medical problems due to enzyme deficiency, but it also causes enormous mental and emotional trauma to the family members of the affected virilized female patient. There is social stigma attached with this condition, with the result that the parents though distressed by the condition of an affected child, may feel shy of seeking medical attention. This is especially the scenario in the conservative societies of our part of the world where disorders of sexual development a considered a taboo.

In this study, we diagnosed 40 cases of congenital adrenal hyperplasia. 80% (32 patients) of these were salt losers. In this group of patients, 23 patients were received in shock. It is a known fact that CAH patients can present with adrenal crisis and shock, usually in the second week of life.[7] This is a life threatening condition unless identified quickly. It is the reason why universal screening for CAH has been advocated and started in developed countries.[6,8] It has been advocated that in absence of neonatal screening, the mortality in cases of CAH is 20-40%[9]. Our finding corroborates this fact that the adverse outcomes in these cases would have been prevented if neonatal screening for CAH would have been a norm in our country.

Recurrent vomitings, dehydration , refusal of feeds and lethargy were the presenting complaints in 20 patients (62.5% of salt losing group). This is the usual presentation in the patients with CAH[10]. In clinical practice, it will be prudent to examine the genitalia of an infant presenting with recurrent vomitings, so that any case of CAH with genital ambiguity and recurrent vomitings is not missed. 8 patients had a history of unexplained sib death, and this was the sole reason for seeking medical attention in two of them. These expired sibs may have been undiagnosed cases of CAH dying from adrenal crisis. This all the more emphasizes the need for neonatal screening for CAH. 19 patients (47.5%) were products of consannguineous marriage. As CAH is an autosomal recessive disorder, there are increased chances of this disorder occuring in babies born out of consanguineous marriages. Similar results were seen by Bhanji et al[11] in their study.

In our study, all the cases with salt losing type CAH had failure to thrive. It is a well known fact that CAH can present with failure to thrive.[12] Thus, CAH should be a differential diagnosis in every case of failure to thrive presenting in infancy. 26 patients in our study had hyponatremia at admission and 17 had hyperkalemia. This is a usual expected finding in cases of CAH due to deficiency of mineralocorticoids.[13] 6 patients were diagnosed to have simple virilizing CAH. Though these patients have less chances of mortality and are picked up earlier due to genital ambiguity, even these cases may suffer adrenal crisis in case of an intercurrent illness.[14] One patient was diagnosed to have CAH during evaluation of precocious puberty. Diagnosis of cases of non-classical CAH may be delayed due to their delayed presentation with precocious puberty.

CONCLUSION

Congenital adrenal hyperplasia is a unique disorder due to very adverse outcomes and even death resulting from enzyme deficiency if left untreated; and associated social taboos resulting in parents shying from seeking medical attention for a child with ambiguous genitalia.there is a need to start neonatal screening for CAH in our country so that deaths due to adrenal crisis in unrecognized patients are prevented.

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ORIGINAL ARTICLE

P-WAVE ABNORMALITIES IN PATIENTS OF STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Introduction: COPD is a common preventable and treatable disease and a major cause of morbidity and mortality globally. ECG is a very simple, widely available and convenient bedside investigation that can be used to detect various cardiac abnormalities. Electrical activities of the heart are often influenced by COPD. ECG changes like P-wave abnormalities have to be carefully assessed before coming to an inference.

Methodology: The present study was an institutional based prospective study, conducted from July 2014 to June 2015. The study was designed to assess the various ECG abnormalities in stable COPD patients and to determine echocardiography findings in relation to ECG changes.

Results: Among the P-wave abnormalities P-wave axis verticalisation (PWAV) was observed in 59(76.6%) patients. Twenty (26%) patients showed negative P-wave in V1, significant-Ptf(P-terminal force) was observed in 3(3.9%) patients. P-mitrale was seen in 18(31.2%), and P-pulmonale in 16 (20.8%) patients.

Conclusion: Though not specific, ECG may reveal various functional and structural abnormalities of the heart in relation to COPD like PWAV. PWAV may be the most commonly seen P-wave abnormalities in COPD patients. Echocardiography findings suggest that presence of P-mitrale is not conclusive of left atrial overload in patients of COPD. Echocardiography should be done routinely in all COPD patients to confirm ECG findings and to diagnose pulmonary hypertension, cor-pulmonale and other subclinical cardiovascular co-morbidities like left ventricular diastolic dysfunction.

Keywords: Chronic obstructive pulmonary disease, ECG, Echocardiography, P-wave axis verticalisation

INTRODUCTION

COPD is an important public health problem and a major cause of morbidity and mortality in both developed and developing countries. Exacerbations and Comorbidities contribute to the overall severity in individual patients.[1] Cardiovascular co-morbidities are particularly common in COPD[2]. In mild to moderate COPD, cardiovascular disease is the leading cause of hospitalization and second leading cause of mortality after lung cancer, contributing to 25% of the total COPD death.[3] However, in advanced COPD, respiratory failure is the main cause of mortality.[4] Screening for cardiovascular co-morbidities should be an important component in the management of COPD as they can worsen the clinical status and prognosis of COPD patients. COPD also influences the electrical events of the heart. ECG is a very simple, widely available and convenient bedside investigation that can be used to detect various cardiac abnormalities in COPD patients.[5] Right atrial enlargement(RAE) may be expressed as P-Pulmonale, P-wave axis verticalisation(PWAV), significant-Ptf (P-terminal force). The frontal PWAV (P-axis > 60°) has a close correlation with emphysema and may be an early finding of worsening of COPD before occurrence of other ECG changes of right heart hypertrophy and enlargement, such as P-pulmonale. Increasing verticality of the frontal P-vector correlates with increasing degree of airway obstruction, degree of depression of the diaphragm and radiographic quantification of the disease.[6-9] The Ptf is one of the P-wave indices affected by COPD, it is considered as a highly specific sign for left atrial enlargement (LAE). Amplitude of i-PV1 >1.5 mm is an established ECG criterion for RAE. The most commonly encountered type of significant-Ptf (s-Ptf) is a fully negative P-wave morphology in V1.[10] Increased Ptf in emphysema may be due to downward right atrial position caused by RA displacement, and thus the common assumption that increased P-tf implies LAE should be made with caution in patients with emphysema. Therefore, s-Ptf and verticalization of P-vectors in emphysema might be a more functional outcome of diaphragmatic depression from severe emphysema rather than RA strain or RAE. The present study was undertaken to evaluate the various

ECG and echocardiographic abnormalities in patients with stable COPD and to correlate ECG abnormalities with echocardiography findings. The objective was to know the influence of COPD on ECG changes by comparing the same with echocardiographic findings with an emphasis on P-wave abnormalities.

METHODOLOGY

Current study was conducted in the department of pulmonary medicine, IGMC, Shimla from July 2014 to June 2015. It was an observational prospective study conducted after prior approval from the ethical committee. We evaluated 77 consecutive patients with stable COPD who attended the outpatient department (OPD) of pulmonary medicine, IGMC Shimla from various places in Himachal Pradesh. All subjects were included in study after obtaining informed written consent. Non-COPD cases like bronchial asthma, pulmonary tubercuosis, lung cancer, interstitial lung disease and bronchiectasis; cases with known co-morbidities like cardiac disease, hypertension, and diabetes mellitus and patient not willing to give informed consent were excluded.The selected patients were subjected to detailed history and thorough clinical examination. We obtained chest radiography, spirometry, ECG of all subjects under study. Echocardiography was obtained in 66 patients. Eleven patients failed to get their echocardiography done. Preand postbronchodilator spirometry was performed as per ATS/ERS recommendations[11] using a spirometer (Spirolab 11) in all subjects to assess the severity of airflow limitation as per GOLD guidelines [Table 1].[1]

A single channel 12-Lead ECG machine (BPL-CARDIART 6108T) was used to record electrocardiographic characteristics. The ECG is recorded on to standard paper travelling at a rate of 25mm/s. The paper is divided into large squares, each measuring 5mm wide and equivalent to 0.2 s. Each large square is five small squares in width, and each small square is 1 mm wide and equivalent to 0.04s. The electrical activity detected by the ECG machine is measured in millivolts. Machines are calibrated so that a signal with amplitude of 1mV moves the recording stylus vertically 1cm. throughout this text, the amplitude of waveforms will be expressed as: 0.1 mV =1mm =1small square. P-pulmonale is a tall and peaked p-wave in standard lead II, III and AVF. P-wave height in lead II will be ≥2.5mm. PWAV is diagnosed by P-wave amplitude in lead III greater than its amplitude in lead I or a negative P-wave in aVL. Significant Ptf is a fully negative P-wave morphology in V1or calculated by multiplying the duration of the terminal negative phase of P-wave in V1 (in milliseconds) by its depth in millimeters. Ptf magnitude of ≥40 mm.ms, along with the presence of IAB (P-wave duration >110 ms), is considered a highly specific sign for left atrial enlargement (LAE). Amplitude of i-PV1 >1.5 mm is an established ECG criterion for RAE. [10]

A conventional echocardiography was performed using "iE33 xMATRIX " Doppler echocardiography system and parameters like Pulmonary hypertension, right atrial enlargement, left atrial enlargement, structural and functional abnormalities of right and left ventricles were noted in relation to ECG changes. Observations and results were statistically compared and analysed on their mutual relations using SPSS20 software. Chi-Square Test is applied to check the independence of variables. Chi-Square Test for independence is applied when we have two categorical variables (e.g. heart rate and severity) from a single population. It is used to determine whether there is a significant association between the two variables. We compared ECG changes with gender, age group, duration of illness, mMRC grades, GOLD stages, smoking status, SI, biomass exposure and BMI. P-value of less than 0.05 was considered statistically significant.

RESULTS

We studied the ECG characteristics in all (77) patients and echocardiography pattern in 66 patients. ECG and echocardiography findings were compared with gender, age group, duration of illness, severity of obstruction (GOLD), smoking status, smoking-index (SI) and biomass exposure. We also compared ECG findings with corresponding echocardiography findings.

Table 1: COPD severity groups by GOLD criteria (Patients with FEV_1/FVC ratio less than 0.7)

GOLD 1	Mild	$FEV_1 \geq 80\%$
GOLD 2	Moderate	$50\% \geq FEV_1 \leq 80\%$
GOLD 3	Severe	$30\% \geq FEV_1 \leq 50\%$
GOLD 4	Very Severe	$FEV_1 < 30\%$

The baseline characteristics of study population with their number and percentage are shown in [Table 2]. More number of patients(46.6%) were in the age group of 60 to 69 years. The mean age of the patients was 64.46 years. Male constituted majority of our study population. There were 58(75.3%) male and 19(24.7%) female with a male: female ratio of 3:1. Study population included patients from various places in and around Shimla and other districts of the state.

Though the duration of illness was varied from less than one year to more than 20 years, majority of the patients i.e., 66(86%) had illness for 1 to 10 years. Sixty seven (87%) of them were smokers.

Table 2: Baseline characteristics of the all study population compared to Patients with P-wave axis verticalisation

Characteristics	Study Population (%) (n=77)	Patients with P-wave axis verticalisation(n=59)
Age in years	Mean=64.46	
40-49	5 (6.5)	3
50-59	12 (15.6)	9
60-69	36 (46.6)	26
70-79	22 (28.6)	20
80-89	2 (2.7)	1
Gender		
Male	58 (75.3)	48
Female	19 (24.7)	11
Duration of Illness in Years		
<1	4 (5.2)	3
01 to 05	49 (63.6)	40
06 to 10	17 (22)	10
11 to 15	4 (5.2)	4
16 to 20	2 (2.7)	1
>20	1 (1.3)	1
mMRC grades		
Grade0	0 (0)	0
Grade1	35 (45.5)	24
Grade2	36 (46.8)	29
Grade3	6 (7.7)	6
Grade4	0 (0)	0
Smoking status		
Never Smoker	10 (13)	6
Ex Smoker	41 (53.2)	29
Current	26 (33.8)	24
Smoking Index		
Nil	10 (13)	6
<100	8 (10.3)	8
100-300	20 (26)	17
>300	39 (50.7)	28
Biomass exposure:		
Present	42 (54.5)	29
Absent	35 (45.5)	30
BMI Range (kg/m2)**:**		
Below normal: <18	31 (40.2)	24
NormalBMI:18-22.9	26 (33.8)	19
Overweight:23.0-24.9	10 (13)	8
Obesity: >25	10 (13)	8
Avg: 14.6-30.4(16.537)		
Severity(GOLD)		
Normal study	8 (10.4)	4
Mild obstruction	11 (14.3)	9
Moderate obstruction	26 (33.7)	20
Severe obstruction	14 (18.2)	11
Very severe obstruction	18 (23.4)	15

Beedi smokers were more prevalent than cigarette smokers. Nearly half of the smokers i.e., 34(44.2%) were heavy smokers with a smoking index of >300. Majority of patients were having rural background and biomass exposure was present in significant number of patients (54.5%).

Table 3: ECG Characteristics of the study population

ECG Characteristics(n=77)	No. (%)
Heart rate/min: (mean: 107.2)	
<60	5 (6.5)
60 to 100	64 (83.1)
>100	8 (10.4)
Rhythm	
Regular	73 (94.8)
Irregular	4 (5.2)
Axis	
Normal	44 (57.1)
Right	18 (23.4)
Left	13 (16.9)
North west	2 (2.6)
P- pulmonale:	24 (31.2)
Ptf-V_1(significant)	3 (3.9)
P-wave axis verticalisation(PWAV)	59 (76.6)
-ve P-wave in V_1	20 (26)
P- mitrale	18 (31.2)
QTc interval	
Normal	37 (48)
Borderline	25 (32.5)
Prolonged	15 (19.5)
Poor R-wave progression(PRWP)	23 (29.9)
Left bundle branch block(LBBB)	5 (6.5)
Left ventricular hypertrophy(LVH)	5 (6.5)
Right bundle branch block (RBBB)	2 (2.6)
Right ventricular hypertrophy(RVH)	8 (10.4)

Exposure to biomass fuel was more prevalent in female (89.5%) and a major contributor in the development of COPD among female particularly in rural areas. All of them had breathlessness as their primary symptom which was graded on the basis of mMRC (modified medical research council) classification. Most of the patients i.e. 71(92.3%) had mMRC grade 1 to 2 dyspnoea because we included only patients with stable COPD. The average BMI was 16.5kg/m^2 which is below normal. COPD patients were categorised into mild, moderate, severe and very severe groups as per GOLD criteria based on post-bronchodilator spirometry. Majority of patients 33.7% had moderate obstruction, whereas 23.4% patients had very severe obstruction. Severe obstruction and mild obstruction were seen in 14(18.2%) and 11(14.3%) patients respectively. Spirometric study was normal in 8 (10.4%) patients.

The ECG characteristics of the study population, with their number and percentage are shown in [Table 3]. Most of the patients (64) had a heart rate varying from 60 to 100 per minute with a mean of 107.2/min. It was observed that age, duration of illness, and mMRC grading had a relation with the heart rate which was statistically significant. Majority of patients had regular rhythm with only 3(3.9%) patients having an irregular rhythm. More than half (57.1%) of the patients had normal axis, 18(23.4%) patients had right axis deviation (RAD) and 13(16.9%) had left axis. Only 2(2.6%) patients had an

axis in the north western region. PWAV was observed in 59(76.6%) patients. Patients with PWAV was compared with various groups, [Table 2] summarises the same with their number and P-values. The frequency among male was significantly higher than female population in the study with 48 male and 11 female. The difference was statistically significant with P-value of 0.026. Other groups showed no statistically significant relation with PWAV.

Table 4: Echocardiography findings in the study population

Echo findings(n=66)	No. (%)
Left atrial enlargement (LAE)	2 (3.0)
Left ventricular enlargement (LVE)	5 (7.6)
Right atrial enlargement (RAE)	21 (30.9)
Right ventricular enlargement (RVE)	23 (34.8)
Left ventricular diastolic dysfunction (LVDD)	52 (76.4)
Tricuspid regurgitation (TR)	46 (70.5)
Pulmonary hypertension (PH) (TR Gradient >30)	32 (56.0)
Right ventricular dysfunction (RVD)	3 (4.5)

Twenty (26%) patients showed negative P-wave in V_1. Ptf-V_1 was measured in patients with positive P-wave in V_1. It was significant only in 3(3.9%) patients. Only one patient had absent P-wave i.e., atrial fibrillation. P-pulmonale was seen in 16 (20.8%) patients. No patient was observed to have Himalayan P-wave (amplitude >9mm). Poor R-wave progression was seen in 23(29.9%) patients. Right ventricular hypertrophy was seen in 8(10.4%) patients. QTc interval was normal in 48%, borderline in 32.5% and prolonged in 19.5%.

On echocardiography right atrial enlargement was present in 30.9% patients, right ventricular enlargement was observed in 34.8%, left ventricular diastolic dysfunction was present in 76.4%, measurable tricuspid regurgitation was observed in 70.5% patients, pulmonary hypertension was present in 56% patients. Right ventricular dysfunction, left atrial enlargement and left ventricular enlargement were not present in significant number. Echocardiography findings are summarised in [Table 4].

DISCUSSION

COPD is an important public health problem and a major cause of morbidity and mortality in both developed and developing countries. Cardiovascular co-morbidities are frequently seen in COPD patients and large studies have shown cardiovascular events as a leading cause of COPD-related mortality.[12-14]

Identification of ECG abnormalities may have significant implications in the management and outcome of patients with COPD. Though ECG can be used to screen various cardiac abnormalities, electrical activities are often influenced by the COPD changes:[5] The voluminous lungs have an insulating effect and there by diminishing the transmission of electrical potentials to the registering electrodes. The heart descends to a lower position within the thorax due to lowering of the diaphragm. This will alter the position of the heart relative to the conventional precordial electrode positions. The right ventricle and the right atrium become compromised due to a reduction of the pulmonary vascular bed and also due to chronic hypoxemia. This will result in RVH and dilatation as well as RAE.

Echocardiography plays an important role in determining cardiac changes in relation to COPD and also to detect subclinical cardiovascular abnormalities. Various studies have been done on ECG and echocardiographic abnormalities in COPD patients.[5,15,16]

Our study included a total of 77 stable COPD patients. Majority of the patients were in the age group of 60 to 69 year with mean age of 64.46 years. Majority of patients in our study were male with a male to female ratio of 3:1.PWAV was observed in significant number of patients i.e., 59(76.6%) among which 48 were male and 11 were female and the difference in their number was statistically significant with P-value of 0.026. The difference may be significant because there was male predominance in the study population and ECG findings may be masked in female because of excess soft tissue over chest compared to male. This finding is also supported by the results observed in relation to BMI. Though the association between BMI and PWAV is not statistically significant, there is definite inverse relation with BMI. We know that electrical activities of heart are better conducted in a lean thin patient than obese patient because of lack of interference by the fat tissue to the electrical waves. We can also say that emphysematous changes may be more prevalent in patients with low BMI.

Chhabra *et al.*[17] reported that PWAV is highly effective for screening emphysema and degree of verticalization provides a gross quantification of the disease. The results also showed an inverse correlation of PWAV with FEV_1. Though in our study the relation of PWAV with FEV_1 was not statistically significant the occurrence was frequent in patients showing obstruction than those showing normal study on spirometry, thus supporting the Chhabra *et al.* reports, but with the current study being prospective we could not infer on the effectiveness of PWAV for screening emphysema.

We know that both significant-Ptf with positive P-wave and negative P-wave in V_1 suggest emphysema and downward right atrial position caused by downward displacement of the diaphragm[10], but 20 (26%) patients showed negative P-wave in V_1 and only 3 (3.9%) patients had significant-Ptf suggesting that

negative P-wave in V_1 is the commonest type of significant-Ptf which is consistent with the reports by Chhabra *et al.*[10]

P-pulmonale indicates right atrial enlargement, it was seen in 24 (31.2%) patients and echocardiography revealed right atrial enlargement in 21patients which is a comparable number. ECG showed P-mitrale in a total of 18 (23.4%) patients, but only one out of 18 showed left atrial enlargement on echocardiography giving an inference that P-mitrale is nonspecific for left atrial enlargement or overload particularly in COPD patients. Similarly Ishikawa *et al.*[18]in their study concluded that twinned peaked P-wave or pseudo P-mitrale is diagnostically non-specific and its mere existence cannot imply the existence of left atrial overload. So P-pulmonale may be a reliable indicator of right atrial enlargement where as presence of P-mitrale is not conclusive of left atrial enlargement in COPD patients.

Thus change in ECG characteristics in COPD patients should be meticulously studied and compared with echocardiography findings as the ECG changes may be due to change in structure of the lung and position of the heart due to COPD rather than cardiac abnormality alone.

CONCLUSION

Cardiovascular co-morbidities are seen frequently in COPD patients and have important prognostic implication. Though not specific, ECG may reveal various functional and structural abnormalities of the heart in relation to COPD. P-wave axis verticalisation, negative P-wave in V_1, significant-Ptf and P-pulmonale are the P-wave abnormalities frequently encountered in COPD patients. Though P-wave axis verticalisation, significant-Ptf, P-mitrale all suggestive of change in structure of the lung and position of the heart due to COPD, P-wave axis verticalisation may be the most commonly seen P-wave abnormality among the three. Negative P-wave in V_1 is the frequently seen type of significant-Ptf. P- pulmonale may be suggestive of right atrial enlargement but presence of P-mitrale is not conclusive of left atrial overload particularly in patients of COPD. Echocardiography should be done routinely in all patients of COPD to confirm ECG findings and to diagnose pulmonary hypertension, cor-pulmonale and other subclinical cardiovascular co-morbidities like left ventricular diastolic dysfunction.

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ORIGINAL ARTICLE

A STUDY OF THE TIMING OF DEATH IN PATIENTS WITH TUBERCULOSIS WHO DIE DURING ANTI-TUBERCULOSIS TREATMENT

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ABSTRACT

Introduction: India has 2.0 million estimated tuberculosis (TB) cases per annum with an estimated 280,000 TB related deaths per year. Understanding when in the course of TB treatment patients die is important for determining the type of intervention to be offered and crucially when this intervention should be given. The objectives of the current study were to determine in a large cohort of TB patients in India: - i) treatment outcomes including the number who died while on treatment, ii) the month of death and iii) characteristics associated with "early" death, occurring in the initial 8 weeks of treatment.

Methodology: This was a retrospective study in C.U.Shah Medical College & Hospital in Surendranagar, Gujarat India. A review was performed of treatment cards and medical records of all TB patients (adults and children) registered and placed on standardized anti-tuberculosis treatment from January 2007 to April 2012.

Results: There were 376 TB patients of whom 41 (11%) were known to have died during treatment. Case-fatality was higher in those previously treated (24%) and lower in those with extra-pulmonary TB (1%).Most of deaths during anti-tuberculosis treatment were early, with 66% of all patients dying in the first 8 weeks of treatment. Increasing age and new as compared to recurrent TB disease were significantly associated with "early death". In this large cohort of TB patients, Most of deaths occurred early after starting anti-TB treatment. Reasons may relate to i) the treatment of the disease itself, raising concerns about drug adherence, quality of anti-tuberculosis drugs or the presence of undetected drug resistance and ii) co-morbidities, such as HIV/ AIDS and diabetes mellitus, which are known to influence mortality.iii) Late stage presentation by patients themselves.More research in this area from prospective and retrospective studies is needed.

Keywords: Tuberculosis, India, Death, Timing of death

INTRODUCTION

National TB Control Programmes (NTPs) routinely report treatment outcomes for patients with tuberculosis (TB). This is reflected in national reports and also annual reports from the World Health Organization (WHO) which provide data on treatment outcomes of TB patients from all countries in the world. Treatment outcomes include death, which is defined as death from any cause occurring during the course of anti-TB treatment. There have been a few publications on the timing of death in patients while on treatment. In sub-Saharan Africa, studies have shown that the majority of deaths occur early during the first 1-2 months of anti-tuberculosis treatment.[1-3] In sub-Saharan Africa, where coinfection with HIV is high, this information has been important for NTPs to plan realistic strategies to reduce death rates during treatment. For example, giving antiretroviral therapy (ART) during the initial phase rather than the continuation phase of anti-tuberculosis treatment is more beneficial in reducing death rates in coinfected TB patients, and is based on a sound knowledge of when HIV-infected TB patients die.[4,5] Similar reports of early deaths have come from more industrialised countries such as Singapore[6], Russia[7] and Taiwan.[8]India, with a total population of 1.2 billion, has a well established national TB control programme, based firmly on the "DOTS" strategy, and treatment outcomes are reported regularly for patients with all types of TB.[9] India has an estimated 2.0 million incident TB cases each year, and an estimated TB-related mortality of 280,000 deaths per annum.[9] Understanding when in the course of TB treatment patients die is important for determining the type of intervention to be offered and crucially when this intervention should be given. Such information might be useful in further reducing case fatality rates among TB pa-

tients. There has been previous work carried out in India between 1999 and 2000 and in 2004 looking at timing of death as part of studies that assessed risk factors for death, failure and default and between 50-65% of deaths were reported to occur within the initial phase of treatment.[10,11] However, each of these studies assessed less than 750 patients. As a result, there were small numbers of patients who died, and the findings may not be representative of the wider or more recent picture of timing of deaths during antituberculosis treatment in India within the Revised National TB Control Programme (RNTCP). The aimof this study was to document the timing of reported death in a large cohort of patients with tuberculosis who die during treatment.The specific objectives were to determine in a defined cohort of TB patients:- i) the treatment outcomes and the number who died while on treatment, ii) the month of death and iii) the characteristics of patients who were recorded as having died early in the initial 8 weeks of anti-tuberculosis treatment.

METHODOLOGY

Study design and setting: This was a descriptive retrospective study based on record reviews and adhered tothe methodological guidelines recommended in the STROBE document on observational studies [12]. The study was carried out in C.U.Shah Medical College, Designated Microscopy Centre (DMCs) in Surendranagar, district of Gujarat, West India.TB treatment is initiated in India in accordance with the RNTCP DOTS strategy and, according to this strategy at the time; patients were placed on one of 2 categories for treatment.[13] The duration of treatment for patients in category I or II varied from 6-8 months. Treatment outcomes were obtained for all patients registered during each quarter, 15 months after the start of treatment.

Participants: All TB patients (adults and children) registered and placed on standardised anti-tuberculosis treatment in quarterly periods from January 2007 to April 2012 in the C.U.Shah Medical College DMCs situated in Surendranagar, Gujarat West India were included in the study.

Source of data, variables and data collection instrument: Data were collected from the TB patient treatment card and follow-up records at the DMC, which in turn were cross checked with RNTCP Tuberculosis Unit TB registers. The following information was obtained:- TB registration number, age, sex, type of TB (Pulmonary TB- PTB and extra pulmonary TB - EPTB), category of treatment and HIV-serostatus. Treatment outcomes were recorded, including death during anti- TB treatment. In those who died, the timing of death was recorded as occurring at 4 week intervals from start to completion of treatment. This questionnaire was subsequently revised, and used to capture all data variables for the study.

Analysis and statistics: Data were entered into an Excel file (MS Excel 2003), and were analysed using SPSS version 18 software. The chi-squared test was used to compare groups while the chi-square for trend was used to examine linear trends. Measures of risk were determined using odds ratios (OR) and 95% confidence intervals, with the level of significance set at $P < 0.05$.

RESULTS

There were 376 TB patients whose mean age was 45 (SD $\pm$ 23) years. The treatment outcomes for all patients and also stratified by type and category of TB are shown in Table 1.

Table 1: treatment outcomes in all TB patients and in relation to type and category of TB, C.U. Shah Medical College DMC Surendranagar, Gujarat, India

All TB Patients	Registered on Treatment (%)	Treatment Success (%)	Death (%)	Default (%)	Transfer out (%)	Failure (%)
NSP	159	113 (71.0)	22 (14.0)	15 (9.0)	01 (1.0)	08 (5.0)
NSN	57	55 (96.0)	02 (4.0)	00 (0.0)	00 (0.0)	00 (0.0)
EP	91	86 (95.0)	01 (1.0)	04 (4.0)	00 (0.0)	00 (0.0)
Previously Treated	69	41 (59.0)	16 (24.0)	05 (7.0)	01 (1.0)	06 (9.0)
Total	**376**	**295 (78.0)**	**41 (11.0)**	**24 (6.0)**	**02 (1.0)**	**14 (4.0)**

Case fatality rates were 11% in patients with both new smear-positive and smear-negative pulmonary TB (PTB). Compared with patients who had new smear-positive PTB, case fatality rates were significantly lower at 1 % in those with extra-pulmonary TB (EPTB) and significantly higher at 24 % in those with previously treated TB on a retreatment regimen.

Most of deaths during anti-tuberculosis treatment were early, with 66 % of all patients dying in the first 8 weeks of treatment. Increasing age and recurrent as compared to new TB cases were significantly associated with "early death".

Table 2: Timing of Death in Patients who were Recorded as Having Died During Anti-Tuberculosis Treatment, C.U. Shah Medical College DMC Surendranagar, Gujarat, India

Deaths Reported From Start of Treatment (In Weeks)	Deaths (%)	Cumulative Frequency (%)
0-4	24 (59.0)	24 (59.0)
5-8	3 (7.0)	27 (66.0)
9-12	7 (17.0)	34 (83.0)
13-16	2 (5.0)	36 (88.0)
17-20	1 (2.0)	37 (90.0)
21-24	2 (5.0)	39 (95.0)
>=29	2 (5.0)	41 (100.0)
Total	**41 (100)**	**-**

Timing of death in all TB patients during the course of anti-tuberculosis treatment is shown in Table 2. Patient characteristics associated with "early deaths" (i.e., dying in the first 8 weeks of treatment) are shown in Table 3.

Table 3: Characteristics of Patients With "Early" Deaths Reported During Anti-Tuberculosis Treatment, C.U.Shah Medical College DMC Surendranagar Gujarat, India

Characteristics	Early deaths < 8 weeks	All deaths during treatment
Gender		
Male	17 (63.0)	29
Female	10 (37.0)	12
Age		
< 14 years	0 (00.0)	00
15-29 years	04 (15.0)	05
30-49 years	13 (48.0)	17
> 50+	10 (37.0)	19
Type of TB		
New smear-+ve PTB	11 (41.0)	22
New smear--ve PTB	02 (07.0)	02
New EPTB	01 (04.0)	01
Previously TreatedTB	13 (48.0)	16
Treatment Category		
Cat 1 (New)	14 (52.0)	25
Cat 2 (Retreatment	13 (48.0)	16
HIV status		
HIV-positive	02 (07.0)	03
HIV-negative	25 (93.0)	38
HIV- status unknown	00 (00.0)	00
Total	27--	41

There was an increased odds of early death associated with age above 30 years, and in new patients and those previously treated cases there was an increased risk of early death.

DISCUSSION

This study in a large cohort of over 376 registered TB patients found a low case fatality at almost 11 %. Patients with previously treated TB had higher death rates and those with EPTB had lower deaths rates than those with new pulmonary tuberculosis. The higher death rates in previously treated patients might be explained by more severe and drug resistant disease consequent upon failed first line therapy or initial and undiagnosed multi-drug resistant TB. [13,14] Although we did not document the types of EPTB during this study, the majority of patients in India with EPTB have lymph node disease,[13] which tends to be associated with morbidity but not mortality. There was a fairly even distribution of deaths during the course of anti-tuberculosis treatment. This is in marked contrast to the situation in sub-Saharan Africa where there is an excess of deaths in the first 1-2 months of treatment, thought to be due to late presentation and therefore severe tuberculosis disease as well as the effects of advanced HIV disease in those who are co-infected. [3,4] The two main characteristics associated with more frequent "early death" in this study were age above 30 years and previously treated disease compared with new disease. Increasing age has been noted as arisk factor for death in other studies both within India[10,15] and outside of India[2], and new disease in contrast to recurrent disease was also associated with high early mortality during the first 4 weeks of treatment in Malawi.[2] Why this occurs is not known. Older people may be at higher risk of comorbid disease which may result in a more serious illness at the time of presentation, diagnosis and treatment, and they may also develop chronic respiratory illnesses resembling and mistaken for smear-negative PTB due to chronic bronchitis and lung cancer.[16] Patients with recurrent disease may also be familiar with the symptoms and signs of TB, and therefore present earlier than those with new disease and as a result have less risk of early death. HIV-serostatus was not associated with "early deaths" in the small sample of patients. Why is there a difference in distribution of deaths in India compared with sub-Saharan Africa?First and most importantly, it will be necessary to repeat this study in other parts of the country and in large numbers of patients to ensure that the results in Andhra Pradesh are nationally representative. If indeed the results are confirmed, then there may be various explanations. India has a problem with initial defaulters[17] i.e., patients who are diagnosed with active TB but fail to get registered and placed on treatment. A high initial default rate will falsely lower early death rates in registered TB patients, obscuring the true picture of patients dying early during the registration and first few weeks of treatment of their disease. Second, HIV co-infection is lower in India than in Africa, with national rates of HIV-infection in TB patients currently at 5-10%.[9] Untreated, advanced HIV disease is therefore not an important factor in India, while in sub-Saharan Africa this has played a major role in case fatality and early deaths, and to some extent this has

been mitigated by the introduction of cotrimoxazole preventive therapy and antiretroviral therapy. If death rates are truly dispersed in an even manner during the course of anti-TB treatment in India then more work needs to be done in this area. Reasons may relate to the treatment of the disease itself, raising concerns about drug adherence, quality of anti-tuberculosis drugs or the presence of undetected drug resistance. They may also relate to co-morbidities which influence mortality. For example, diabetes mellitus has been calculated to account for 15%-20% of pulmonary TB in India,[18] and there is growing evidence that diabetes is associated with an increased case fatality in TB patients.[19] The timing of death in diabetes patients who have TB is not known and requires active research, but one could speculate that diabetes exerts its negative effects throughout the course of anti-TB treatment as a result of drug-drug interactions, an increased association with anti-tuberculosis drug toxicity and immune suppressive effects of diabetes. The strengths of this study are that there were a large number of patients enrolled in the cohort and treatment outcomes were tracked and recorded using standardised systems. However, there are a number of limitations. First, this was a record review and it is possible that mistakes were made in the recording of timing and date of death. Second, patients who are recorded as default or transfer out may also have died[15], and such misclassification may affect the results. Third, the records that formed the source of data did not contain valuable information such as results of any culture and drug sensitivity testing, which might have been important in explaining reasons for some of the deaths. Whatever the shortcomings of this study, the results should serve to encourage others to repeat similar studies in other parts of the country and should also encourage programme staff to carefully record timing of death and timing of other adverse events such as default and transfer out. A number of potentially important measures might help to reduce death rates by ensuring that i) all patients diagnosed with smear-positive sputum are registered and start anti-TB treatment as soon as possible (thereby cutting down initial default rates), ii) patients who are at risk of drug resistance, such as those previously treated, have culture and drug sensitivity testing so that treatment is appropriately tailored to levels of drug resistance, and iii) elderly patients are investigated for co-morbidities including diabetes mellitus which may increase the risk of death during treatment. A better understanding of when and why the estimated 280,000 annual TB-related deaths occur is essential as India strives to improve programme performance and exceed the new 2015 global targets of treatment success rates of 90% in the years to come.

CONCLUSIONS

In this large cohort of TB patients registered in Surendranagar, Gujarat West India, deaths occurred with an even frequency throughout anti-TB treatment. Reasons may relate to i) the treatment of the disease itself, raising concerns about drug adherence, quality of anti-tuberculosis drugs or the presence of undetected drug resistance and ii) co-morbidities, such as HIV/AIDS and diabetes mellitus, which are known to influence mortality. More research in this area from prospective and retrospective studies is needed.

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ORIGINAL ARTICLE

STUDY OF PLATELET RICH PLASMA INJECTIONS IN PATIENTS OF TENDINOPATHY IN SOUTH GUJARAT POPULATION

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ABSTRACT

Introduction: Tendinopathy is a major medical problem associated with sports and physical activity in active people over 25 years of age. We study about the effect of PRP in the patients of chronic Tendinopathy.

Methods: From the patients of chronic tendinopathy who failed medical treatment for last 3 months, platelet rich plasma is prepared from patient's own blood. After giving platelet rich plasma injection, patient is advised to take rest for 3 weeks with analgesics. Physiotherapy is started after 3 weeks of injection as this is causing pain for first 3 weeks. Patients are advised to join their duty after 3 weeks of injection. All the patients were followed up in OPD at 3 weeks, 6 weeks, 3 months and 6 months. At every follow up, range of motion, visual analogue scale and functional activity score recorded.

Results: The follow up shows that most of the patients do not get relief within 3 weeks after injection. Follow up shows that 16 patients out of 50 got relief within 6 weeks after injection. Result shows that 46 patients out of 50 get relief within 6 months after injection. That means 94% of patients are having relief within 6 months of injection.

Conclusion: The findings of this study shows that platelet rich plasma injection under ultrasound guidance at the tendon is effective mode of treatment for patients and takes time but result in gradual decrease in symptoms.

Keywords: Chronic tendinopathy, platelet rich plasma

INTRODUCTION

Tendinopathy is a major medical problem associated with sports and physical activity in active people over 25 years of age. It can be defined as a syndrome of tendon pain, localized tenderness, and swelling that impairs performance.[1]The clinical diagnosis is determined mainly through the history, although the exact relationship between symptoms and pathology remains unknown. In chronic tendinopathy, there is an increasing degree of degeneration with little or no inflammation present. Increasing age results in decline of the ultimate load of the muscle–tendon–bone complex, ultimate strain, as well as modulus of elasticity and tensile strength of the tendon. The application of PRP has been documented in many fields.[2] First promoted by M. Ferrari in 1987 as an autologous transfusion component after an open heart operation to avoid homologous blood product transfusion, there are now over 5200 entries in the NCBI for PRP ranging in fields from orthopedics, sports medicine, dentistry, otolaryngology, neurosurgery, ophthalmology, urology, wound healing, cosmetic, cardiothoracic and maxillofacial surgery. We study about the effect of PRP in the patients of chronic Tendinopathy at Govt. Medical College, Surat

The objective of the study was to know the efficacy of platelet rich plasma in chronic tendinopathies like tennis elbow, golfer's elbow, supraspinatus tendinopathy, patellar tendinopathy, tendo achilles tendinopathy and plantar fasciitis and also to evaluate the outcomes of this recent modality of treatment for chronic tendinopathies. The objective was also to study advantages and complications of platelet rich plasma in tendinopathy and long term relief of pain in chronic tendinopathies.

METHODOLOGY

This was a prospective study undertaken in the Department of Orthopedics Government Medical College, Surat. Patients with chronic tendinopathy came to New Civil Hospital, Surat included in the study after obtaining their informed consent and

Clearance from institutional ethical committee was obtained. The patients with not improved with medical treatment for last 3 months with or without physiotherapy included in the study.

A detail history was obtained for evaluating the mode of trauma, visual analogue score, chronicity, physiotherapy etc. Detail clinical examination and investigations were carried out before giving injection. The inclusion and exclusion criteria were as follows.

Inclusion Criteria: Patient with symptoms typical to Lateral and medial epicondylar tendinopathy, supraspinatus tendinopathy, tendoachiles tendnopathy, plantar fasciitis, patellar tendinopathy. Treated with diclofenac 100 mg twice a day or Ibuprofen 400 mg thrice a day or tramadol 100 mg twice a day and physiotherapy for more than 3 months but not improved

Exclusion Criteria: Any skin pathology at local site, Symptoms < 3 months duration, Patients who have taken chronic anti platelet therapy like in stroke, myocardial infarction etc., Patients having muscular dystrophy, Patients having more than one chronic tendinopathies.

After getting informed consent platelet rich plasma was prepared from patient's own blood. After giving platelet rich plasma injection, patient was advised to take rest for 3 weeks with analgesics. Physiotherapy was started after 3 weeks of injection as this was causing pain for first 3 weeks. Patients are advised to join their duty after 3 weeks of injection. The visual analogue scale and functional activity score is recorded just after giving injection.

All the patients were followed up in OPD at 3 weeks, 6 weeks, 3 months and 6 months. At every follow up, range of motion, visual analogue scale and functional activity score recorded. When the patient has started his/her duty, was recorded. Check for development of any complication. The data thus obtained was entered in a spread sheet and analysed using independent sample t test for quantitative variables, paired t test for paired observations and chi square test for categorical observations. Value of less than 0.05 was considered significance level and all the values below it was considered as statistically significant.

RESULTS

The mean age of study group was 38 years for the male. The mean age of study group was 40 years for the female. There was no significant difference between the age of males and females. Fifty percent of males and females belong to 31 - 40 years, 70% of males and females belong to 31 - 50 years. The chronic tendinopathy was more common in form of tennis elbow and plantar fasciitis. 66% of patients are having plantar fasciitis and tennis elbow. Golfer's elbow was more common in males than females. In this study, patellar tendinopathy was not seen in females.

The follow up shows that most of the patients do not get relief within 3 weeks after injection. The mean of males who got relief within 3 weeks is 0.2 with standard deviation of 0.4. The mean of females who got relief within 3 weeks is 0 with standard deviation of 0. Only 1 patient of planter fasciitis got relief from pain at 3 weeks. Pain relief was considered when visual analogue scale of the patient decreased to at least 50% from preinjection visual analogue scale.

Follow up shows that 16 patients got relief within 6 weeks after injection. Patients with planter fasciitis, tennis elbow, golfer's elbow and patellar tendinopathy seem to get pain relief earlier as compared to patients with supraspinatus tendinopathy and tendoachilles tendinopathy. . Pain relief was considered when visual analogue scale of the patient decreased to at least 50% from preinjection visual analogue scale. At 12 weeks 37 patients out of 50 get pain relief is considered when visual analogue scale of the patient decreased to at least 50% from preinjection visual analogue scale.

Result shows that 46 patients out of 50 get relief within 6 months after injection. That means 94% of patients are having relief within 6 months of injection. Pain relief was considered when visual analogue scale of the patient decreased to at least 50% from preinjection visual analogue scale. It shows that all the patients with planter fasciitis, golfer's elbow, supraspinatus tendinopathy and patellar tendinopathy have relief from pain. But in tennis elbow 82% of patients had significant relief from pain and in tendoachilles tendinopathy 80% patients had significant relief from pain.

Table 1: Distribution of patients returning to their work after injection

Time	Male	Female	Total
Within 1 month	1	0	1
Within 2 month	14	2	16
Within 3 month	27	10	37
Within 6 month	32	14	46

Table 1 shows the duration returning to work by patients after injection. It shows that 74% of patients returned to their work after 3 months and 92% of patients within 6 months of injection. This table gives the idea regarding the relief of pain to the patients.

Table 2: Distribution of patients as per VAS

VAS	Preinjection	At 3 weeks	At 6 weeks	At 12 weeks	At 6 months
≥ 70	46	40	10	4	2
50 – 69	3	7	26	9	3
20 – 49	1	3	14	28	7
< 20	0	0	0	9	38
Total	50	50	50	50	50

Table 3: Distribution of patients as per FAS

FAS	Preinjection	At 3 weeks	At 6 weeks	At 12 weeks	At 6 months
2	46	43	18	6	2
1	4	7	31	38	16
0	0	0	1	6	32
Total	50	50	50	50	50

Table 4 Quality of PRP Compared with Results

Quality of PRP [increase in concentration compared to the baseline platelet count]	Cases	Result			
		Excellent	Good	Fair	Poor
< 3.5	15	04	06	03	02
3.5-5.5	30	28	2	0	0
>5.5	05	05	0	0	0

Table 2 shows Visual Analogue Scale (VAS) of patients having chronic tendinopathy. This table shows that pain is gradually decreasing over the time. Within 3 weeks only 10 patients got relief from pain, while within 6 weeks approximately 40 patients got relief. This suggest that Platelet Rich Plasma injection acts gradually over the time.

Table 3 shows Functional Activity Score (FAS) of patients having chronic tendinopathy. This FAS shows the routine daily activity carried out by a person. Table shows that within 3 weeks there is less improvement compare to 6 weeks. And at the end of 6 months almost all the patients can perform their daily activity smoothly.

This table suggest that quality of platelet count in platelet rich plasma has impact on the result. This table suggest that when the platelet count in platelet rich plasma injection is less than 3.5 times to the baseline level, 33% patients had fair to poor result. When the platelet count in platelet rich plasma injection is between 3.5 to 5.5 times to the baseline level, significant pain relief found in all patients. When the platelet count in platelet rich plasma injection is more than 5.5 times to the baseline level, all the patients have excellent result in chronic tendinopathies.

Table 5 Distribution of patients as per the result

Result	Male	Female	Total
Excellent	25	12	37
Good	6	2	8
Fair	1	2	3
Poor	1	1	2
Total	33	17	50

The Visual Analogue Scale is less than 20 then the result is excellent; if VAS is between 20 to 49 then the result is good; if VAS is between 50 - 69 then the result is fair and if VAS is greater than 70 then the result is poor.

Table shows the result of patients after 6 months of treatment. Table shows that 90% of the patients got excellent to good results with significant relief in pain; 6% of the total patients had fair result where as 4% of the total patients had poor result with minimal relief in pain.

31 male patients were having significant pain relief out of 33 patients and 14 female patients were having significant pain relief out of 17 females. So in male 94% of patients having pain relief as compared to female which is 82%. There were no major complications observed in the study apart from local pain at injection site. Also there was no side effect to patients due to this treatment.

DISCUSSION

The mean age of the study group in male was 38 years with a standard deviation of 9.7 years. The mean age of female was 40 years with a standard deviation of 9 years. This study is almost comparable with Volpi et al in which the mean age of the study group was 40 years in male and 39 years in female. This study is also comparable with Mishra and Pavelko et al having mean age of 41 years in male and 42 years in female.

In this study, the duration of follow up examintaion is of 6 months which was comparable to Thanasses et al and Ferrero et al study. But in Volpi et al and

Mishra and Pavelko et al study are having follow up period of 2 years.[3,4]

In this study, pain and function improvement were found at 8 weeks after injection. So this study is comparable to Mishra and Pavelko et al and Volpi et al in which pain and functions were improved at around 8 weeks of injection. But in Ferrero et al study, improvement in pain occurs at around 3 weeks and in Thanasses et al study, pain improvement was found at 6 weeks.[5]

Mishra and Pavelko noted the significant improvement in PRP group for pain at 8wk and at 24months, 93% in VAS score and function . Thanasas noted significant improvement in VAS at 6 weeks. Volpi noted improvement of symptoms in 80% of patients. Hechman noted that PRP improves function and pain obviating the need for surgery.[6]Rha noted the improvement in pain and function after 3 months of injection.[7]Barret and Erredge noted that 77.8% of patients were successfully treated. Six patients achieved complete resolution of pain within 2 months.[8] In this study significant improvement was found in pain and function in 80% of patients at 8 weeks. In all the above studies, PRP injection was given under ultrasonography guidance except in Mishra an Pavelko study and Hechmen study. Though the PRP injection was given at the precise site under ultrasonography guidance, it had similar result as compared to PRP injection which were given blindly in other studies.

Table 6: Comparison Mean age in different Studies

Study	Mean age	
	Male	Female
Volpi et al	40	39
Mishra and Pavelko et al	41	42
This study	38	40

Table 7: Comparison of studies of platelet rich plasma in chronic tendinopathies

Study	Indication	Follow up period	Outcome
Mishra and Pavelko et al	Chronic Tennis Elbow Golfer's Elbow	2 years	Significant improvement in PRP group for pain at 8wk and at 24months +93% in VAS score and function
Thanasas et al	Chronic Tennis Elbow Golfer's Elbow	6 months	Significant improvement in VAS at 6 weeks
Volpi et al	Chronic Tennis Elbow Golfer's Elbow Patellar Tendinopathy Tendoachilles Tendinopathy	2 years	Improvement of symptoms were found in 80% of patients
Hechman et al	Chronic Tennis Elbow Golfer's Elbow	6 months	PRP improves function and pain obviating the need for surgery
Rha et al	Supraspinatus Tendinopathy	6 months	Improvement in pain and function after 3 months of injection
Barret & Erredge	Plantar Fasciitis	12 months	77.8% of patients were successfully treated. Six patients achieved complete resolution of pain within 2 months
This Study	Tennis Elbow Golfer's Elbow Plantar Fasciitis Patellar Tendinopathy Tendoachilles Tendinopathy Supraspinatus Tendinopathy	6 months	Significant improvement in pain and function found in 80% of patients at 8 weeks

In this study, 74% of patients were able to return to their work at around 10-12 weeks of injection; 92% of patients were able to return to their job within 6 months. In 80% of patients, pain reduced significantly within 8 weeks and in 92% of patients pain reduced within 6 months of injection.

CONCLUSION

The findings of this study show that platelet rich plasma injection under ultrasound guidance at the tendon is effective mode of treatment for patients with chronic tendinopathies. This suggest that

platelet rich plasma injection takes time to act and this will result in gradual decrease in symptoms. Platelet rich plasma is very effective in treatment of chronic tendinopathies. So, one should consider this treatment before going to surgical treatment for chronic tendinopathies. One of the limitations was that the study was carried out with 6 months of follow up only; long term results and follow up would have been ideal. Also the sample size could have been larger so that it could be applied over the population and comparing it with another modality of treatment for chronic tendinopathy. This study aids to the current knowledge of administration of PRP injection in orthopedics.

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ORIGINAL ARTICLE

A RETROSPECTIVE, MOLECULAR STUDY OF EGFR AND ALK MUTATIONS IN NON SMALL CELL LUNG CANCER PATIENTS

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ABSTRACT

Background: Epidermal growth factor receptor EGFR/ALK mutations are the strongest response predictors to EGFR tyrosine kinase inhibitors (TKI) and ALK inhibitor respectively, but knowledge of the EGFR/ALK mutation frequency on lung adenocarcinoma is still limited.

Methodology: Our study is a retrospective study of the metastatic non small cell lung cancer patients harboring EGFR/ALK receptors. A total of 94 metastatic non small cell lung carcinoma patients data were evaluated, out of which 74 patient's EGFR&ALK mutation status was known.

Results: All of the patient's data evaluated in this study were in the age group of 30-74.Total 74 patient's EGFR &ALK mutation status was known, out of which 34.2% were positive for EGFR and 4% for ALK respectively. In EGFR positive group 62.96%were male and 37.04% were female. Among males patients 34% were positive for EGFR as compared to 42% of EGFR Positive female patients.

Conclusion: Efforts to obtain tissue samples should be encouraged for *EGFR*&ALK mutation testing in non small cell lung carcinoma patients to provide a molecular basis to treat patients with available targeted therapy.

Keywords: EGFR, ALK, Non Small Cell Lung Cancer

INTRODUCTION

Lung cancer is the most common cancer and cause of cancer related deaths all over the world. The lung cancer represents 13 percent cases of all new cancer cases and 19 percent of cancer related deaths worldwide. In 2012, 1.8 million new lung cancer cases were detected[1].Lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 per cent of all cancer related deaths in India. It is the most common cancer and cause of cancer related mortality in men.[2] Our understanding of disease biology has evolved over the years. The histological classification is now stretching to molecular classification. Newer molecular targets and driver mutations which play a major role in the pathogenesis have been identified.[3] Metastatic non-small cell lung cancer (NSCLC) patient's treatment historically consisted of systemic combination chemotherapy. Chemotherapy generally kills cells that are growing or dividing; it causes symptomatic improvement, improves quality of life, and improves survival in some patients with NSCLC.[4]

An improved understanding of the molecular pathways of lung is very essential, knowledge molecular pathway has led to the development of agents that target specific molecular pathways in malignant cells at the same time sparing of normal cells, like mutations in the epidermal growth factor receptor (EGFR) or rearrangements of the anaplastic lymphoma kinase (ALK) gene.[5] There are many targeted therapies available in lung cancer against these mutations, most of are administered as orally-available small molecule kinase inhibitors.[6] The identification of these mutation positive patient has led to an ongoing effort to identify biomarkers and treatments that can be used for other subsets of patients with advanced NSCLC. In NSCLC, and in other malignancies, Identification of driver mutation and treatment with targeted therapy specific to that for an individual patient has resulted in significantly improved therapeutic efficacy, often in conjunction with decreased toxicity.[7]

We have done a retrospective record based study of EGFR/ALK mutation status in lung cancer patients.

The primary objective of the study was to assess the overall *EGFR /ALK* mutation frequency. Secondary objectives were to investigate the correlation between *EGFR /ALK* mutation status and demographic and clinical factors**.**

METHODOLOGY

Study design-We Retrospectively evaluated the data of metastatic non small cell lung carcinoma patients

coming to Sri Aurobindo Institute of Medical Sciences(SAIMS) Indore . Study duration was four months from January 2016 to April 2016

All the medical records of patients coming between July 2013 to March 2016 were evaluated for EGFR and ALK mutation status as well as demographic and clinical characteristics of the patients in respect to age , sex, socioeconomic status ,metastatic lesions and smoking history. Patients with unknown receptor status and with incomplete information were excluded from the study.Paraffin embedded tissue blocks obtained by biopsies or surgically resected specimens, from primary tumors as well as from metastatic sites, were analysed for mutation analysis. Genomic deoxyribonucleic acid was extracted and exons 18-21 of EGFR gene were amplified by polymerase chain reaction (PCR).The amplified PCR product was subjected to the direct nucleotide sequencing for the detection of mutations. ALK mutation analysis was done by Fluorescence in situ hybridization (FISH).

RESULTS

Our study was a retrospective study from July 2013 to March2016. Total 94 patients were registered out of which 74 patients were evaluated for EGFR/ALK mutation analysis.Overall demography/clinical characteristics for the Patient population are summarized in **Table 1**.

Table 1: Key Demographic and Clinical Characteristics

Variable	No. (%)
Age,Median (range)	57(30-74)
Sex %	
Male	50 (68.00)
Female	24 (32.00)
Smoking History	
Smoker	45 (61.00)
Non smoker	29 (39.00)
Metastasis	
Liver	20 (27.00)
Brain	10 (14.00)
Bones	54 (73.00)
Others	34 (46.00)
Exposure while cooking(Females)	
Exposure	10 (42.00)
No Exposure	14 (58.00)
Back ground	
Rural	40 (54.00)
Urban	34 (46.00)

Demographic and clinical data shows that median age was 57 years (Range, 30–74y).out of total patients ,32% patients (24 of74) were female, Total 61% patients had a smoking history, interestingly in female subgroup 42% females had a history of exposure to smoke while cooking food. Background data shows, 58% patients with rural as compared to 42 % of patients with urban background. Most of the patients had bone mets (74%) followed by liver (27%).

Total 34.2% **(Table.2)** patients were positive for EGFR mutation and 4% were positive for ALK mutation. On sub group analysis of EGFR Mutation positive patients, 66% patients were non smoker. In the subgroup of ALK Mutation patients, only 1 patients (33%) was smoker.

Table 2: Stratification of EGFR /ALK Mutation

Variable	EGFR POSIITVE	ALK POSITIVE
Median age (range)- 57(30-74)	34.2%	4%
Sex%		
Male	17(34%)	2(67%)
Female	10(42%)	1 (33%)
Cooking exposure	5(19%)	0
Smoking history		
Smoker	9(33%)	1(33%)
Never smoker	18(67%)	2(67%)
Occupational exposure %	8(30%)	0

DISCUSSION-

Diagnostic work-up for NSCLC includes driver mutation screening, and the information obtained by such diagnostic workup is useful in choosing standard therapy according to the mutation status. Upfront targeted therapies in driver mutation positive NSCLC, whereas conventional chemotherapy in the absence of driver mutation. In a French study of lung cancers by molecular profiling, 50 percent of tumors exhibited a genetic alteration, which led to use of targeted agent as first-line therapy in half of these cases.[8] Advanced NSCLCs containing characteristic mutations in EGFR/ALK are highly sensitive to EGFR /ALK TKIs. Erlotinib has shown better response rates and PFS as compared to conventional chemotherapy for first line treatment in EGFR mutation positive advanced NSCLC.[9-10]

Crizotinib, a tyrosine kinase inhibitor targeting ALK, has shown a response rate of 65 per cent in previously treated patients of NSCLC that harbour ALK rearrangement and has been approved for this indication.[11-12] Multiple reliable techniques are available to assay for EGFR/ALK mutations, and these are feasible on formalin fixed tissue.[13] Mutations in the EGFR tyrosine kinase are observed in approximately 15 percent of NSCLC adenocarcinoma in the United States and occur more frequently in women and nonsmokers. In Asian populations, the incidence of EGFR mutations is substantially higher. In our study the EGFR mutation rate was 34.2%, which is higher compared to EGFR mutation rate in western lung cancer population.In the PIONEER study, which is

an Asian study.[14] The incidence of EGFR mutations ranged from 22 to 62% (51.6%).Although EGFR mutations were more common in nonsmokers, still the incidence was 37 percent in regular smokers. The frequency of such mutations was higher in women than in men. EGFR mutation rate in our study falls in the range of Asian PIONEER study. Among non smokers, 67 percent were positive for EGFR mutation in our study. Whereas 60.7 percent non smoker patients were positive for EGFR mutation in PIONEER study. So majority of the patients were non smoker in the EGFR mutation positive group.

The frequency of EGFR mutation positive rate was higher in females (42%) compared to males (34%),which is also comparable with PIONEER study. Where 61% females were positive for EGFR mutation as compared to 44 % male population in PIONEER study. In female EGFR positive sub group analysis,19 percent females had a history of exposure to smoke while cooking food in rural areas. Occupational exposure was associated with 30 percent of EGFR Positivity. Generally, female sex, adenocarcinoma histology, never-smoking status, and Asian ethnicity are considered the most important factors associated with *EGFR* mutation and response to EGFR-TKIs.[15]

In unselected NSCLC populations, the ALK rearrangement is a relatively rare event. The overall incidence of ALK gene rearrangements in subsequent series has been about 4 percent. Except in rare cases, the presence of ALK gene rearrangements in NSCLC tumors tends to occur independent of epidermal growth factor receptor (EGFR) or KRAS mutations. Similar frequencies of ALK gene rearrangements have been reported in Asian and Western populations.[16]In our study out of 74 patients, only 4% were positive for ALK Mutation. Among ALK Positive patients majority (67%) were males and Non smoker (67%) which is comparable to other studies.Our study is the first study in central India highlighting the *EGFR /ALK* mutation status.

In summary, the observed frequency of tumor *EGFR and ALK* mutation in demographic and clinical subgroups of patients in our study suggests that *EGFR*&ALK mutation testing should be done not only in female and non smoker patients but also in males and smokers, particularly in Asian populations Such an approach should help ensure the optimal identification and treatment of patients whose tumors harbor *EGFR* /ALK mutations.

CONCLUSION

EGFR &ALK mutation testing should be encouraged upfrontly in metastatic non small cell lung cancer patients to provide a molecular basis to treat patients with available targeted therapy.

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ORIGINAL ARTICLE

OUTCOME OF LOW MAINTENANCE DOSE MGSO4 IN ECLAMPSIA PATIENTS OF A TERTIARY CARE HOSPITAL OF GUJARAT, INDIA- A PROSPECTIVE STUDY

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ABSTRACT

Background: Eclamptic convulsions are life-threatening emergencies and require proper treatment to decrease maternal morbidity and mortality. Amongst the principles of management of eclampsia, the first and foremost is the control of convulsions. In the last decade researchers in developing countries (like India) are constantly striving to steadily decrease the doses of MgSo4 regimes in view of decrease the toxicity of MgSo4 therapy.

Methodology: Present study was a prospective interventional study and hdsanalysed all antenatal, intranatal and postnatal cases diagnosed as eclampsia and admitted to Obstetric ward, HDU, ICU (medical and surgical), IMC of Shree Krishna Hospital and Pramukhswami Medical college, Karamsad. All patients of Eclampsia admitted in the hospital during the study period were included in the study. Patients fulfilling the inclusion criteria, MgSo4 4gm was administered slowly intravenously over 10-15 minutes as loading dose and maintenance dose 0.5g/hr continue up to 24 hrs of delivery or 24hrs after convulsions whichever was later. Those patient were developed recurrent convulsion, they were given 2g MgSo4i.v. stat and maintenance dose was converted in standard dose 1g/hr.

Results: In the present study we could achieve the average serum magnesium level around 3.3-3.4 mEq/L. These were below therapeutic range for eclampsia but within the range of normal blood level. Even serum magnesium level in subtherapeutic range, 89.2%patients had not developed recurrent convulsions. 33(71.73%) patients delivered Vaginally and 13(28.26%) were delivered by LSCS. Most common indicationsfor LSCS were fetal distress in 1st stage of labour followed by severe oligohydroamniosis and failure of induction of labour.

Conclusion: Low maintenance dose of magnesium sulphate therapy is effective for controlling convulsion in cases of eclampsia. The toxicity is reduced to nil. There was no maternal complication due to recurrent convulsions because patient was under close monitoring and immediately the stepping up of dose was enough.

Keywords: Eclampsia, MgSo4, Stillbirth, LSCS

INTRODUCTION

Hypertensive disorders of pregnancy are unpredictable Multiorgan disorder unique to human pregnancy. Pregnancy Induced Hypertension has been a recognized pathological entity since the time of Hippocrates and ancient Greeks complicating 5-20% pregnancies.

Convulsions in preeclampsia that cannot be attributed to any other factor defined as Eclampsia. Hypertensive disorders are important cause of maternal and fetal morbidity and mortality. Approximately 1,00,000 women die worldwide annually because of eclampsia, A majority of these maternal deaths occur in low-income countries where the quality of maternity care is often inadequate.[1]

Eclamptic convulsions are life-threatening emergencies and require proper treatment to decrease maternal morbidity and mortality. Amongst the principles of management of eclampsia, the first and foremost is the control of convulsions.

Implementation of MgSo4 would be strengthened if guidelines and recommendations for practice could be based on reliable evidence about the comparative effects of alternative regimens. Regimens for administration of MgSo4 have evolved over the years, but have not been formally evaluated.[2]It is therefore rel-

evant to assess the pros and cons of alternative strategies for administration. It is particularly important to assess the minimum effect dose and duration of treatment.

In the last decade researchers in developing countries (like India) are constantly striving to steadily decrease the doses of MgSo4 regimes in view of decrease the toxicity of MgSo4 therapy, limitation of trained staffs for its administration and monitoring of patients during MgSo4 therapy, our Indian women who on an average weigh much less than the western women and decrease the cost oftreatment in poor resource countries.

The present study was undertaken with an objective of assessing efficacy and toxicity of low maintenance dose of MgSo4in the treatment of eclamptic women with low weight or body mass index in our institute

METHODOLOGY

Present study was a prospective interventional study and hdsanalysed all antenatal, intranatal and postnatal cases diagnosed as eclampsia and admitted to Obstetric ward, HDU, ICU (medical and surgical), IMC of Shree Krishna Hospital and Pramukhswami Medical college, Karamsad. The study was reviewed and permitted by Institutional Human Resource Ethics Committee.

Study Period: 1st May 2012 to 30th June 2013 (i.e. 14 months).

Inclusion Criteria: Antenatal, intranatal, and postnatal women with appearance of convulsion without other causes was diagnosed as eclampsiaand patients who were weighing less than 50 kg by visual estimate.

Exclusion Criteria: It includes pregnancy with other causes of seizures were excluded such as known case of epilepsy and weight of patient>50kg.

Subject recruitment: All consecutive subjects fulfilling the inclusion criteria were taken in the study.

After admission the main aim was to prevent further convulsions, to control hypertension, and to stabilize the patient.

Patients fulfilling the inclusion criteria, MgSo4 4gm was administered slowly intravenously over 10-15 minutes as loading dose and maintenance dose 0.5g/hr continue up to 24 hrs of delivery or 24hrs after convulsions whichever was later. Those patient were developed recurrent convulsion, they were given 2g MgSo4i.v. stat and maintenance dose was converted in standard dose 1g/hr.

Serum magnesium level were measured three times. First within 30 mins of starting MgSo4 therapy, 2nd after 4 hours of therapy and 3rd after 8 hours of therapy.

Measures were taken to prevent aspiration & asphyxia due tongue fall during convulsions. Oxygen support was given. Foley's catheterization was done.

Clinical parameters measures toxicity of MgSo4 are i) Deep tendon reflex, ii) Respiratory rate, and iii) Cardiac rhythum

Antihypertensives (like Labetalol, Nifedipine or Nitroglycerine nitrate) were used to controlsevere hypertension and were administered as intermittent to keep diastolic blood pressure at about 90 mmHg as per department protocol.

Obstetric management was carried out after stabilizing the patient.

Patients with unfavorable cervix but adequate pelvis were induced for labour after cervical ripening with misoprostol. And LSCS were done according to obstetric indications.

Those admitted in labour without contraindication for vaginal delivery were monitored continuously on CTG and delivered vaginally.

RESULTS

This is a Prospective study of 46 cases of eclampsia at Pramukhswami Medical College, Karamsad, Anand from May 2012 to June 2013(i.e. 14 months)

Table 1: Status of patients with respect to receiving loading dose of MgSo4 (n=46)

Status of patients	No. (%)
Adequate loading dose	15(32.61)
Inadequate loading dose from outside)	10(21.74)
No treatment from outside	11(23.91)
Direct Emergency Admission	10(21.74)

Table 2: Maintenance Dose of MgSo4 in gm/hr (n=46)

Maintenance Dose	No. (%)
0.5	40 (86.96)
0.5 to 1	5 (10.87)
0.5 to 0.3	1 (2.17)

Table 3: Serum magnesium level in meq/L

Sample	Mean (sd)
30 mins after loading dose of MgSO4 therapy	3.40 (1.2)
4 hours after starting of MgSo4 therapy	3.32 (0.8)
8 hours after starting of MgSo4 therapy	3.30 (0.7)

sd=Standard Deviation

Table 1 shows that only Out of total 46 patients, 15(41.66%) of referred patients received adequate

loading dose of MgSo4 treatment before referral.In our institute, loading dose 4gm IV MgSo4 was given in 31(67.39%) patients on admission followed by maintenance dose.

Table 4: Total MgSo4 Dose (gm)(n=46)

Total MgSo4 Dose(gm)	No. (%)
<=20	23 (50.00)
21-25	8 (17.39)
26-30	7 (15.21)
31-35	5 (10.86)
36-40	1 (2.17)
>40	2 (4.34)

Table 5: Mode of Delivery (n=46)

Mode of Delivery	No. (%)
Vaginal Delivery	31 (67.39)
Instrumental Vaginal Delivery	2 (4.34)
LSCS	13 (28.26)

Table 6: ICU admissions and Ventilator support

Critically ill patients	No. (%)
I.C.U admissions	6 (13.04)
Ventilator support	
Non invasive	2 (4.34)
Invasive	3 (6.52)

Table 7: Perinatal outcome (n=46)

Perinatal outcome	No. (%)
Live Births*	39 (84.78)
Still Births	8 (17.39)
Neonatal death	5 (10.87)
Term Delivery	20 (43.47)
Preterm Delivery	17 (36.95)
Immature Delivery	2(4.34)
Low Birth Weight	31 (65.95)
IUGR	7 (15.21)

*One twin delivery

Table 2 shows that, all patients were given Low maintenance dose 0.5gm/hr of MgSo4intravenously by infusion pump.Amongst them, 5(10.87%) patients required to be increased maintenance dose from 0.5 to 1 gm/hr because of recurrent convulsion. In 1(2.17%) patient, maintenance dose was decreased from 0.5 to 0.3gm/hrdue to decreased urine output (<30ml/hr) where knee jerk was present.

Table 3 shows mean value of serum magnesium level of all patients at three different time.

Therapeutic range of serum magnesium is expected as 4-7 meq/L.[3]

Table 3 shows that in the present study we could achieve the average serum magnesium level around 3.3-3.4 mEq/L. These were below therapeutic range for eclampsia but within the range of normal blood level. Even serum magnesium level in subtherapeutic range, 89.2%patients had not developed recurrent convulsions.

Table 4 shows that total MgSo4 dose required in therapy was less than 30 gms in 38(82.6%) of patients. Recurrent Convulsion Rate was 10.8% in the present study. There was no toxicity due to MgSo4 threapy in the present study.

After admission, all antepartum and intrapartum patients were actively managed.25(69.44%) patients were induced for labour when bishop score was less than 5 by tab misoprost25 ug pervaginally and repeated 4hrly.Augmentation of labour was done when cervix was 3-4 cm dilated byArtificial rupture of membrane andOxytocin drip (2-30 mIU/min)

Table 5 shows that 33(71.73%) patients delivered Vaginally and 13(28.26%) were delivered by LSCS. Most common indicationsfor LSCS were fetal distress in 1st stage of labour followed by severe oligohydroamniosis and failure of induction of labour.

Table 6 shows that Critical care in the form of I.C.U. admission(13.04%) and ventilator support (10.88%) wererequired in patients with Acute pulmonary edema, Dilated cardiomyopathy, Aspiration pneumonia and PRESS syndrome in our institute.

Table 7 shows that8(17%) patients had Stillbirth and 5(10.6%)patients had Neonatal deaths, therewere 4 preterm deliveries.Perinatal Mortality ratio in the present study is33.33 per 1000 live births.

Total31 (65.95%) babies out of 47 babies were <2.5 kg weight and 15.21% babies had IUGR reflecting the effect of eclampsia in fetal growth restriction as well as its role in higher incidence of preterm delivery emphasizing the importance of good antenatal care in preventing the same.

DISCUSSION

Total 46 patients were treated during the study period. The dose of MgSo4 given in first 24hrs was significantly less in present study.

Table 8 shows comparison of different studies with respect to Reduction from the standard dose.the dose of MgSo4 given in first 24hrs was significantly less in present study. The reduction from Pritchard standard dose was 58.9% which was higher than any other studies.

Achievement of maintenance serum magnesium level:- i.e. The lower limit of target plasma magnesium level as mention by Brian J. Koos[84] is about twice the physiologic concentration which is around 1.7 mEq/L .In the present study we could achieve the average magnesium level around 3.3-3.4 mEq/L.

Table 8: Total MgSo4 Dose Required in Study.

Studies	Loading dose IM/IV	IM/IV maintenance dose	Total MgSo4 Dose (gm) in first 24 hrs	Reduction from the standard dose
Pritchad et al.,[4]	4 g IV plus 5+5 g IM	5g / 4hrlyIM	39	Standard dose
Bhalla et al.,[5]	4g IV plus 4+4g IM	4g/4hrlyIM	32	18%
Zuspan et al,[6]	4g IV	1 g/hr IV	28	28.3%
Begum et al.,[7]	4g IV plus3+3g IM	2.5g/4 hrlyIM	22.5	42.3%
N. Jana et al.,[8]	3g IV plus2.5+2.5gIM	2.5g/4hrlyIM	20.5	47.4%
Sumansardesai et al.,[9]	4g IV	2g /3 hrlyIM or IV	20	48.8%
Present study	4g IV	0.5 g/hr IV	16	58.9%

Table 9: Comparison of Serum Magnesium level in mEq/L

	Present study(Mean serum mg level) mEq/l	Begum et al.,[7](Mean serum mg level) mEq/l
1stSample	3.4(within 30 mins of loading dose)	2.97 (5 mins after loading dose)
2ndSample	3.32(4 hrs after loading dose)	2.78(4 hrs after loading dose)

Table 10: Comparison of Recurrent convulsion rate and Maternal mortality with different regimes of MgSo4 therapy.

Author	Regimen	Recurrent convulsion	Maternal mortality
Pritchard et al.,[4]	Pritchard	12 %	0.4 %
SumanSardesai et al.,[9]	Low dose MgSo4	7.8 %	2.6 %
Begum et al.,[7]	Dhaka regimen	1.53 %	8.6 %
Mahajan et al.,[10]	Padhar regimen	1.05 %	-
Chowdhury etal.,[11]	Low dose maintenance	2 %	3.3-5 %
Eclampsia trial group[12]	Eclampsia trial group	5.3-13.2 %	3.8-5.2 %
Joshi et al.,[13]	Single Dose MgSo4	9.16 %	3.3 %
Ekele et al.,[14]	Ultra short regimen	7.4 %	9.9 %
Present Study	Low dose Maintenance	10.8 %	0

Table 11: Comparison of Perinatal mortality ratio

Author	Year	PMR(%)
Joshi et al., Bellary, Karnataka.[13]	2003-2007	24.9
Nousheen Aziz et al., Hyderabad.[15]	2007	45.00
Bangal V et al., Loni.[16]	2009	33.0
S Singh et al., Berhampura, Orissa.[17]	2011	47.00
Manjusha S et al., Pune, Maharastra.[18]	2011-2012	26.08
Present study	2012-2013	33.33

Table 10 shows that overall mortality was ranging from 0.4 to 9.9%. None of patient died in low maintenance therapy which was a remarkable observation.

Table 11 shows that PMR was 33.33% in the study which was comparable to other studies. And ranging 24.9 % to 47% in different studies.

CONCLUSION

At conclusion of present study , it is clear that low maintenance dose of magnesium sulphate therapy is effective for controlling convulsion in cases of eclampsia in patients weighing around 50kg (BMI 25 or less). The toxicity is reduced to nil. So drug therapy becomes very safe and the patient who got recurrent convulsion after therapy could be controlled by 2 gm (20% solution) IV loading dose followed by 1 gm IV maintenance dose. There was no maternal complication due to recurrent convulsions because patient was under close monitoring and immediately the stepping up of dose was enough. One important observation is that convulsions were under control in our patients with subtherapeutic level of magnesium. This needs further research.

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ORIGINAL ARTICLE

A STUDY ON CORRELATION OF CAROTID INTIMA AND MEDIA THICKNESS WITH STRESS ECG AND 2D ECHO IN TYPE 2 DIABETES MELLITUS PATIENTS IN TERTIARY CARE HOSPITAL OF PUNE CITY

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ABSTRACT

Background: The atherosclerotic process in diabetes mellitus causes intimal thickening and luminal narrowing. The present study was conducted with an objective to study correlation of Carotid Intima and Media Thickness with Stress ECG and 2D Echo in type 2 DM.

Methodology: This cross-sectional study was conducted on cases of asymptomatic type 2 DM. A detailed history was taken and clinical examination consisting of all diabetic manifestations including carotid bruit and other peripheral vascular disease was noted. All patients were subjected to necessary laboratory investigations, stress ECG and 2D Echo.

Results: Among the 50 DM cases, there was no significant correlation found between CIMT and Age (P value>0.05). There was significant correlation found between CIMT (group ≤0.9 - ≥0.7) with sex and duration of DM with p value <0.05. There was significant correlation found between CIMT (group ≤0.9 - ≥0.7) with BMI, Waist Circumference, Waist to Height Ratio with p value <0.05. There was no significant correlation found between CIMT and 2D Echo findings at p value >0.05.

Conclusion: We concluded from this study that CIMT could be positively correlated with sex, duration of DM, BMI, Waist Circumference, WHR, BSL, and HbA1c. However, CIMT could not be correlated with age, urine protein, diabetic retinopathy, and 2D Echo findings.

Keywords: Type 2 Diabetes Mellitus, carotid intima and media thickness, 2D Echo

INTRODUCTION

Diabetes Mellitus (DM) is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[1] In etiologic classification-it's mainly divided in type 1 DM and type 2 DM. Type 2 DM is most common form of diabetes. Most patients with type 2 DM are obese when they develop DM and obesity aggravates insulin resistance. The risk of Type 2 DM increases with age, obesity, hypertension, dyslipidemia and physical inactivity. Dyslipidemia is responsible for atherosclerosis which causes macro vascular complications and micro vascular vasculopathy.[2]

Atherosclerosis involves several processes starting in the artery wall and ultimately leading to impaired blood flow to the cardiac muscle, brain, peripheral organs, causing ischemia, or infarction. The atherosclerotic process causes intimal thickening and luminal narrowing. The rupture of the overlying intima or endothelial erosion leads to exposure of the atherosclerotic lesion contents to platelets and initiates thrombosis.[1]

Some non invasive tools have been shown to be clinically useful to obtain measures of arterial function and morphology, including measurement of Carotid Intima and Media Thickness (CIMT), stiffness, pulse wave velocity and arterial compliance. However, there are very limited studies reporting CIMT and stiffness measurement in Indians who differ from the western population in cardiovascular risk profile, morbidity, and mortality.[3] The present study was conducted with an objective to study correlation of Carotid Intima and Media Thickness with Stress ECG and 2D Echo in type 2 DM.

METHODOLOGY

The present study is the cross-sectional study conducted on cases of asymptomatic type 2 DM cases admitted to Medicine section (OPD and Wards) of Dr.D.Y.Patil Medical College, Hospital and Research Centre, Pimpri, Pune. The study was conducted from period of August 2013 to September 2015. The diagnosis of type 2 DM was established in patients ≥40 years of age by fasting plasma sugar >126mg/dl or random/postprandial plasma sugar >200mg/dl or HbA1c >6.5 in cases having symptoms of polyuria and polydipsia. A pre-designed semi-structure questionnaire was utilized for data collection. A detailed history was taken and clinical examination consisting of all diabetic manifestations including carotid bruit and other peripheral vascular disease clinically was noted. All patients were subjected to necessary laboratory and radiological investigations. The cases with Type 1 DM, Hypertension, Dyslipidemia, Cardiomyopathy, Pericardial diseases, Existing Ischemic Heart Disease, Rheumatic Heart Disease, Large and medium vessel vasculitis, both primary and secondary, known smokers and/or tobacco chewers, known ECG abnormalities like conduction disturbances, Pre Excitation syndrome, Patients already on statins and anti platelets drugs are excluded from the study. Institute Ethics committee clearance was obtained before starting the study. Written informed consent was taken from all patients involved in the study.

RESULTS

There were 50 cases of type 2 Diabetes mellitus included in the present study. Relationship between age, gender and duration of diabetes with CIMT is shown in Table 1. There was no significant correlation found between CIMT and Age with P value>0.05. There was significant correlation found between CIMT (group ≤0.9 - ≥0.7) with sex and duration of DM with p value <0.05.

Table 1: Age, gender and duration of diabetes distribution among study participants

Variable	CIMT ≤0.9-≥0.7	CIMT<0.7	Total	P value
Age (Yrs)				
40 – 49	11	8	19	>0.05
50 – 59	6	5	11	
60 – 69	10	6	16	
>69	3	1	4	
Sex				
Male	21	8	29	<0.05
Female	9	12	21	
Duration of DM				
<1	5	5	10	<0.001
1 – 5	6	13	19	
≥ 6	19	2	21	
Total	**30**	**20**	**50**	

Table 2: Distribution of cases according to physical parameters

Parameter	CIMT ≤0.9-≥0.7 (n=30) Mean±±SD	CIMT<0.7 (n=20) Mean±SD	p-Value
Body Mass Index	29.13±4.67	26.58±3.15	<0.05
Waist Circumference	90.27±7.48	83.95±7.99	<0.01
Hip Circumference	99.83±4.078	100.95±3.953	>0.05
Waist to Hip Ratio	0.91±0.081	0.83±0.083	<0.005

Table 3: Laboratory profile of the cases

Parameter	CIMT≤0.9 – ≥0.7 (n=30) Mean±SD	CIMT<0.7 (n=20) Mean±SD	p-Value
BSL-fasting	181.37±33.303	159.90±20.807	<0.05
BSL-PP	307.80±73.104	257.60±37.867	<0.01
HbA1c	8.29±1.116	7.24±0.537	<0.005

Table 4: Urinary protein level of the cases

Urine protein	CIMT ≤0.9 - ≥0.7	CIMT<0.7	Total
1+	20	10	30
2+	3	0	3
3+	1	0	1
Normal	6	10	16

P value >0.05

Table 5: Association between diabetic retinopathy and CIMT

Retinopathy	CIMT ≤0.9-≥0.7	CIMT <0.7	Total
Proliferative Diabetic Retinopathy	2	0	2
Non-proliferative Diabetic Retinopathy	23	11	34
Normal	5	9	14
Total	30	20	50

P value >0.05

Table 6: Association between 2D ECHO and CIMT

2D ECHO finding	CIMT ≤0.9-≥0.7	CIMT <0.7	P-Value
Mild Conc LVH	2 (6.67)	4 (20)	>0.05
AVS	3 (10)	1 (5)	>0.05
MAC	2 (6.67)	1 (5)	>0.05
Diastolic dysfunction	1 (3.33)	0	>0.05
RWMA	0	0	
Normal	24	16	

There was significant correlation between CIMT (group ≤0.9 - ≥0.7) with BMI, Waist Circumference, Waist to Height Ratio with p value <0.05 (Table 2)

There was significant correlation found between CIMT (group ≤0.9 - ≥0.7) with BSL-fasting, BSL-PP and HbA1c at p value <0.05 (Table 3). There was no significant correlation found between CIMT (group ≤0.9 - ≥0.7) with Urinary protein secretion at p value

<0.05 (Table 4). There was no significant correlation found between CIMT (group ≤0.9 - ≥0.7) with diabetic retinopathy at p value <0.05 (Table 3)

There was no significant correlation between CIMT and 2D Echo findings at p value >0.05 (Table 6)

DISCUSSION

In our study, we observed cases with duration of diabetes grouped as duration <1 yr, 1-5 years, and 6 years and above, with mean duration of 4.68 years. There was significant correlation between CIMT and duration of diabetes, with p value of 0.001. Robin et al[4]observed that the CIMT increased with the duration of diabetes with a significant p value of 0.02. Similar results were obtained in a Chennai based study and Mohan Rema et al[5]who observed increase in CIMT with increasing duration of diabetes.

There was significant correlation observed between CIMT and BMI with p value <0.05. But no significant correlation was observed between Body Mass Index and carotid CIMT in similar studies by R Gayathri[6] and Tanmay Jyoti Sau[7]. The CIMT was found to be higher among those with central obesity as assessed by the waist circumference and waist-hip ratio with a significant P value of <0.01 and <0.005 respectively. R Gayathri et al[6] observed waist hip ratio to be an independent determinant of CIMT. Frouse et al[8] also demonstrated positive correlation between WHR and carotid wall thickening.

There was significant correlation found between CIMT and BSL-F and BSL-PP with p value <0.05 and <0.01 respectively.R Gayathri et al[6] observed significant correlation between BSL-F and CIMT. Thomas R Einarson et al[9], demonstrated significant correlation between BSL-PP and CIMT.However, Bernd Kowall et al[10] did not find any correlation between BSL and CIMT. There was significant correlation found between CIMT and HbA1c with p value <0.05.Similar observations were found in a studies conducted by Matsumoto et al[11] and R Gayathri.[6]

There was no correlation found between CIMT and 2D Echo findings with p value >0.05.Adler et al[12] showed significant association between the presence and severity of MAC and aortic atheroma.Luca Sgorbini[13] found significant correlation between CIMT and MAC values.A similar study[14] showed a strong association between aortic valve sclerosis and systemic endothelial dysfunction which was evaluated by ultrasonography of the brachial artery.

CONCLUSION

We concluded from this study that CIMT could be positively correlated with sex, duration of DM, BMI, Waist Circumference, WHR, BSL, and HbA1c. However, CIMT could not be correlated with age, urine protein, diabetic retinopathy, and 2D Echo findings. A large population study is recommended to find out the prevalence of asymptomatic Coronary artery disease amongst type 2 DM with CIMT >0.9mm.

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ORIGINAL ARTICLE

EMPIRICAL TREATMENT IN CLINICALLY DIAGNOSED CASES OF VITAMIN B12 DEFICIENCY

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ABSTRACT

Background: Vitamin B12 deficiency may present with fatigue, weakness, numbness, decreased memory, irritability, confusion and depression, although initial symptoms might often be vague. Even though the human body can store vitamin B12 to last for up to five years, its deficiency is not very uncommon. The diagnosis is frequently made on the basis of a costly tests like low serum vitamin B12 level or megaloblastic bone marrow or both. This study was aimed to measure the effect of Empirical treatment in clinically diagnosed cases of Vitamin B12 deficiency.

Methodology: Current study was a prospective study, done in a private hospital. All patients attending OPD during July 2015 to December 2015 forms the study population.

All patients full filling inclusion criteria and willing to give informed written consent were treated with 2ml Intramuscular injection of Vit B 12 1000mcg thrice a week for total ten injections. Follow up of patients were done on weekly basis for first month, then every two weekly for next two month and then monthly basis for next three months. After this period, symptoms were reassessed and recorded.

Results: Total 90 clinically suspected patients of Vitamin B12 deficiency were willing to participate in the study. Out of total 90 patients, 39 (43.33%) patients were male and 51 (56.67%) patients were female. Out of total 90 patients, maximum number of patients i.e 31 (34.44%) were from age group of 41 to 50 years. All symptoms were significantly improved after completion of standard course of Vit B12. In out of total 90 patients having complain of generalized weakness, improvement was observed in 83 (92.22%) patients. Out of total 88 patients having complain of myalgia and 84 patients having complain of paresthesia, improvement was recorded in 76 (86.36%) and 73 (86.9%) patients respectively.

Conclusion: We conclude and recommend from the study that diagnosis based on clinical assessment is reliable. Thus, in resource poor country like India diagnosis should be advocated on symptoms of Vit B12 deficiency and empirical treatment should be suggested.

Keywords: Vitamin B12, Paresthesia, Myalgia, Depression

INTRODUCTION

Vitamin B12 is essential for synthesis of s-adenosyl methionine and is involved in the metabolism of proteins, phospholipids and neuro transmitters. Its deficiency leads to several neurological manifestations and affects all age groups.[1] Vitamin B12 deficiency may present with fatigue, weakness, numbness, decreased memory, irritability, confusion and depression, although initial symptoms might often be vague.[2,3,4]

Even though the human body can store vitamin B12 to last for up to five years, its deficiency is not very uncommon. The diagnosis is frequently made on the basis costly tests of of a low serum vitamin B12 level or megaloblastic bone marrow or both.[5,6]

Vitamin B12, apart from causing neuropsychiatric symptoms, leads to hyperhomocysteinemia and methylmalonic acidemia which can have serious health implications. Low serum vitamin B12 levels have low sensitivity and specificity in terms of tissue deficiency. Homocysteine and methylmalonic acid estimations are adjunct and aid in diagnosis of B12 deficiency but still serum vitamin B12 measurement is the extensively applied standard method by practical purposes.[7]

But all tests that diagnose Vitamin B12 deficiency are much more costly and after diagnosis had made, cost

of treatment also added. On the other hand symptoms of Vitamin B12 are having large spectrum and it can be easily suspected by experienced clinician. Even standard therapeutic dose does not have any side effect in normal individual. Thus in resource poor settings like in India, empirical therapy of Vitamin B12 without testing of Vit B12 levels or methylmalonic acid (MMA) can be advocated.

This study was aimed to measure the effect of Empirical treatment in clinically diagnosed cases of Vitamin B12 deficiency.

METHODOLOGY

Current study was a prospective study, done in a private hospital of Ahmedabad, Gujarat. All patients attending OPD during July 2015 to December 2015 forms the study population.

Inclusion criteria:

Patients full filling all of the following criteria were included in the study

1) Age >18 years.

2) Patients having at least four of the following symptoms/signs at the time of presentation. These signs/symptoms include generalized fatigue, paresthesia, myalgia, loss of appetite, confusion, tremor, labored breathing, depression.

3) Patients not having medical and surgical comorbidities that hinder vitamin B 12 absorption (e.g. Celiac disease, Crohn's disease, pernicious anemia, tuberculosis, long term use of acid reducing durgs, diabetes medication metformin users, parasite infections, people who have undergone certain surgical procedures in the gastrointestinal tract.)

4) Patients willing to give informed written consent.

Suspected depression patients were referred to psychiatric OPD to confirm the diagnosis. And those full filling inclusion criteria referred back to orthopedic dept.

Patients not giving written consent were excluded from the study without affecting routine management.

All patients full filling inclusion criteria and willing to give informed written consent were treated with 2ml Intramuscular injection of Vit B 12 1000mcg thrice a week for total ten injections. Follow up of patients were done on weekly basis for first month, then every two weekly for next two month and then monthly basis for next three months. After this period, symptoms were reassessed and recorded.

There were total 122 patients having symptoms likely of B12 deficiency and full filling inclusion criteria. Out of these, 15 patients refused to give informed written consent. Out of remaining 107 patients, 17 patients were become loss to follow up till the end of the study. Thus, total 90 patients remained in the study till the end.

Data were entered in Microsoft Excel and analysed using Epi Info software.

RESULTS

Total 90 clinically suspected patients of Vitamin B12 deficiency were willing to participate in the study. All patients were prescribed standard treatment for Vitamin B12 deficiency.

Table 1: Age and Gender wise distribution of Vit B12 deficient patients

Age	Male (%) (n=39)	Female (%) (n=9)	Total (%) (n=90)
20-30	4 (10.26)	7 (13.73)	11 12.22)
31-40	10 (25.64)	8 (15.69)	18 (20.00)
41-50	16 (41.03)	15 (29.41)	31 (34.44)
51-60	5 (12.82)	12 (23.53)	17 (18.89)
>60	4 (10.26)	9 (17.65)	13 (14.44)
Total	39 (100)	51 (100)	90 (100)

Table 2: Improvement in symptoms after completion of empirical treatment

Symptoms	Improved (%)	Not Improved (%)	Total (%)
Generalized fatigue	83 (92.22)	7 (7.78)	90 (100)
Myalgia	76 (86.36)	12 (13.64)	88 (97.78)
Paresthesia	73 (86.90)	11 (13.10)	84 (93.33)
Loss of appetite	64 (78.05)	18 (21.95)	82 (91.11)
Tremor	34 (72.34)	13 (27.66)	47 (52.22)
Confusion	28 (82.35)	6 (17.65)	34 (37.78)
Laboured breathing	8 (80.00)	2 (20.00)	10 (11.11)
Depression	5 (62.50)	3 (37.50)	8 (8.89)

Table 1 shows that out of total 90 patients, 39 (43.33%) patients were male and 51 (56.67%) patients were females. Out of total 90 patients, maximum number of patients i.e 31 (34.44%) were from age group of 41 to 50 years. Out of total 39 males, maximum number of patients i.e. 16 (41.03%) were from the age group of 41 to 50. In females also same trend was observed. Another common age groups were 31 to 40 years (20.0%) and 51 to 60 years (18.89%). Thus, it was observed that age group of 31 to 60 years attributed to 73.33% patients. This trend was common in both the gender.

Table 2 shows improvement in symptoms after completion of empirical treatment of clinically suspected patients of Vit B12 deficiency. It was observed that out of total 90 patients, all patients were having generalized fatigue. Another common symptoms were myalgia (97.78%), Paresthesia (93.33%)

and Loss of appetite (91.11%). Tremors and confusion were found in 52.22% and 37.78% patients. Least common symptom were Laboured Breathing and Depression which were found in 10 (11.11%) and 8 (8.89%) patients.

All symptoms were significantly improved after completion of standard course of Vit B12. In out of total 90 patients having complain of generalized weakness, improvement was observed in 83 (92.22%) patients. Out of total 88 patients having complain of myalgia and 84 patients having complain of paresthesia, improvement was recorded in 76 (86.36%) and 73 (86.9%) patients respectively. All other symptoms were also significantly improved after completion of treatment.

DISCUSSION

The deficiency state has a very wide presentation and can cause or exacerbate neuropsychiatric and other vague symptoms. In early stage vitamin B12 deficiency might present with subtle and slight cognitive impairments. Hence early recognition becomes crucial for preventing irreversible damage.

Our study stated that 41 to 50 years of age group was the most common age group. It is contrary to other studies which documented that patients having age of > 60 years are most commonly affected. [8] This indicates the changing trend in age group of Vit B12 deficiency. This finding needs to further research. A few other investigators have also refuted age associated decline of vitamin B12 levels.[9-12]

Our study shows female preponderance among patients of Vit B12 deficiency. Same finding were reported by many studies. [8,10,11]

Vitamin B 12 deficiency is common in our country especially in vegetarian population. Many centers in our country still have no facility to estimate serum Vitamin B 12 and very costly in private health sector. We had seen in our results that after giving Inj. Vit B 12 empirically in clinically suspected vitamin B12 patients all the symptoms were significantly improved after completion of standard course of Vit B12. Out of total 90 patients, around 86% patients improvement of all symptoms were recorded after completion of treatment.

CONCLUSION & RECOMMENDATION

Females were commonly affected with Vit B12 deficiency. Diagnosis based on clinical assessment is reliable. Thus, in resource poor country like India diagnosis should be advocated on symptoms of Vit B12 deficiency and empirical treatment should be suggested.

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CASE REPORT

ACUTE EMBOLIC CEREBRAL ISCHEMIA AS AN INITIAL PRESENTATION OF POLYCYTHEMIA VERA

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ABSTRACT

Patients with Polycythemia vera (PV) are at high risk for vaso-occlusive events including cerebral ischemia. Ischemic stroke may be the first presenting symptom of PV in 15% or more of those affected. It had been previously assumed that cerebral ischemic events were due to increased blood viscosity and platelet activation within the central nervous system arterial vessels. However, there are now a few isolated case reports of probable micro-embolic events originating from outside of the brain.

Case report: A 45-year old man presented with left sided hemiperesis (recovered within 12 hours) in our Medicine OPD. Hematologic investigation revealed a hyperviscous state (Hemoglobin 21.9gm% and PCV 66%). Acute infarction in right corona radiata and basal ganglia was found in magnetic resonance imaging(MRI) of brain. Although unusual, acute embolic cerebral ischemia may be an initial presentation of PV. The etiology of stroke in polycythemic patients is likely to be multifactorial. All clinicians involved in the care of stroke patients should be aware of the association of PV and ischemic stroke.

Keywords: Polycythemia vera, Cerebrovascular stroke, Embolic

INTRODUCTION

Polycythemia vera is the clonal stem cell proliferation of red blood cells, white blood cells and platelets. The clinical manifestations of polycythemia vera are mainly due to increased productions of red blood cells and platelets. Increased production of white blood cells does no lead to any significant effects.[1] Clinical presentation of polycythemis vera can be varied. Some people are diagnosed incidentally on hematological work while others can present with complications like stroke, deep vein thrombosis and pulmonary embolism.[1] Ischemic stroke may be the first clinical presentation in 15% of those affected with the disease.[2] It has been assumed that the reason for ischemic stroke in majority of cases of polycythemia vera is platelet activation and thrombus formation in cerebral arteries.[3,4] Some studies have also suggested embolism as the cause of cerebral stroke in cases of polycythemia vera. Here we are presenting a case report polycythemia vera who presented as transient ischemic attack.

CASE REPORT

A 45-year old male presented to the Emergency Department with history of acute onset of left sided weakness involving both upper and lower limb. There was no history of sensory dysfunction. Patient also had intermittent complain of headache and diminission of vision. Patient's brother also had similar complains of headache and diminission of vision. There was no history of diabetes or hypertension.

On examination, vitals were stable and blood pressure was normal. Cranial nerves 2–12 were all intact, speech was fluent without aphasia or dysarthria. Motor examination shows decrease power and tone in left side. Deep tendon reflexes were exaggerated over left side. There was no sensory dysfunction. Respiratory and cardiovascular system examination was unremarkable.

Laboratory investigations revealed Hemoglobin of 21.9, PCV was 66, TLC was 6300, Platelet count was 1.72, RBC count 7.03, MCV 93, MCH 31, RDW 17, Reticulocyte Count was 0.5%, LDH 600 and Uric acid was 4.4. Chest X ray and ECG were normal. MRI Brain revealed small acute infarct in right corona radiate and basal ganglia.

Patient improved completely within 12 hours and thus was diagnosed of having Transient ischemic attack. Detailed investigations were carried out to find out the etiology.

Serum erythropoeitin level was 3.64(3.7-30).CT Abdomen and 2D ECHO was normal.PFT was normal. Karyotype was normal and DNA PCR study for JAK2 mutation was negative. Bone marrow examina-

tion was suggestive of hypercellular marrow with increase in tri-lineage haematopoiesis. Thus a diagnosis ofPolycythemia vera presenting as acute embolic cerebral ischemia was made.

Patient was given IV fluids and Phlebotomy done. Gradually patient's Hemoglobin and PCV came to 14.5mg% and 45% respectively.

DISCUSSION & CONCLUSION

Incidence of Polycythemia vera is around 0.6- 1.6 per million population. It is most common in the age group of 50-70 years.[5] Increase in hematocrit the major factor responsible of increase in viscosity leading to decreased cerebral blood flow. [4,6] Local effect of increased hematocrit, increased viscosity, stagnation of blood and thrombocytosis lead to thrombus formation which is the most common mechanism of cerebral ischemia in polycythemia vera.[4,6] Another proposed mechanism is the emboli formation of which there are only few published case reports.[7,8] In our case patient presented with acute embolic cerebral ischemia and responded well with hemodilution and phlebotomy.

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CASE REPORT

RAPID RECOVERY AFTER EARLY INITIATION OF PLASMAPHERESIS IN ATYPICAL HUS: A CASE REPORT

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ABSTRACT

We report a case of a thirteen year old female diagnosed as aHUS, complicated by malignant hypertension and central nervous system involvement. The patient was treated with plasmapheresis(plasma exchange) and corticosteroids along with supportive care. The patient showed remission immediately and recovered after four weeks of hospital stay and three months later is well on antihypertensives.

Keywords: Plasmapheresis, HUS, Microangiopathic haemolytic anemia, Eculizumab

Abbreviations:

aHUS: Atypical Hemolytic Uremic Syndrome CRP: C- Reactive Protein; USG: Ultrasonography FFP: Fresh Frozen Plasma; LDH: Lactate Dehydrogenase ESRD: End Stage Renal Disease; RBC: Red Blood Corpuscle HPF: High Power Field; CAPD: Continuous Ambulatory Peritoneal Dialysis HD: Hemodialysis; ANA: Antinuclear Antibody; ASO- Anti-Streptolysin Titer

INTRODUCTION

World wide prevalence of aHUS ranges from 2.7-5.5 per million population with an incidence of 0.40 per million. Only 5-10% patients of HUS present with atypical form of HUS. It is a rare, life-threatening and progressive disease with a high mortality and morbidity[1]. A major cause of aHUS is the complement alternative pathway dysregulation[2], leading to arteriolar and inter-lobular arterial involvement causing end-organ damage[3].The complement system may be activated by the mutations in the complement regulatory proteins (factor H, factor I, or membrane cofactor protein) or by acquiring neutralizing autoantibody inhibitors of the components of complement system (anti-factor H antibodies)[1]. The patients may present with signs and symptoms of acute kidney injury, hypertension, encephalopathy, pancreatitis, lung complications, seizure, coma and others.[1,4,5]

We report a case of a thirteen year old female child with aHUS, complicated with hypertension, encephalopathy and seizure, and her therapeutic management.

CASE REPORT

A thirteen year old female child presented with a three day history of abdominal pain, low grade fever and vomiting. There was no history of loose motions/diarrhea or bloody stools. Past or family history is not contributory. Her laboratory evaluation showed Hb 9.8 gm%, Platelets 54000/c.mm. USG abdomen was normal. On the third day of admission, she developed headache, gross hematuria and oliguria (Urine output 0.7ml/kg/hr). This time the laboratory evaluation showed microangiopathic haemolytic anemia (Hb 6.8 gm%, Serum bilirubin 1.4 mg/dl, Serum LDH 2967 U/L, schistocytes 12-15% and Coomb's test negative), thrombocytopenia (platelet count 43000/c.mm) and acute renal insufficiency (Blood urea 137mg/dL, serum creatinine 3mg/dL). Her urine analysis revealed protein 4+, RBC >8-10/HPF and was positive for hemoglobinuria. Her serum C_3 level was found to be low 0.65g/L (Normal 0.9-1.8), ANA was negative, ASO titre was <200 and CRP was non-reactive. Malarial parasite and Dengue titers were negative. USG abdomen revealed stage I Medullary Renal disease. Hence she was diagnosed as D negative HUS (aHUS).

We started with plasmapheresis (plasma exchange) with FFP on sixth day of admission. We started first cycle with 20ml/kg of FFP and then increased to 35ml/kg for next four cycles. These were done on a daily basis. Patient showed signs of improvement after the third cycle. The plasmapheresis was stopped as the platelet count (1.64 x 10^3 / cmm) and serum

LDH (505 U/L) improved[2]. Complete hematological and renal recovery was found after five days of plasmapheresis. Our patient had hematological recovery on day eleven of admission. On day fifteen, she developed malignant hypertension and seizure, and she was put on a several antihypertensives (propranolol, nifedipine, prazosin, hydralazine, nitroglycerine) and anti convulsants (phenytoin sodium, phenobarbitone).

We had also put our patient on pulse methyl prednisolone therapy (three days) followed by oral prednisolone from day ten onwards. Oral prednisolone was continued for a month and stopped with gradual tapering.

We obtained the CFH antibody titre(anti-factor H autoantibodies) from AIIMS, New Delhi. It was found to be 2252 AU/ml. (Normal = <150 AU/ml). Genetic testing was not done due to its cost factor. This was only of diagnostic importance as the patient had already recovered. The lowest hemoglobin recorded was 3.6 gm%, lowest platelet count was 36000/c.mm, peak reticulocyte count was 6.4%, peak urea level was 150 mg/dL, and peak creatinine level reached was 3.6 mg/dL. Our patient had complete remission and was discharged on two antihypertensives after a total of four weeks of hospital stay.

After three months, on follow-up, the patient is stable and her laboratory reports are – Hb 13.3 gm%, Platelet count 2.15 x 10^3/cmm, Serum LDH 569 U/L, Serum creatinine 0.7mg/dL and blood urea is 27mg/dL. Her blood pressure is also well controlled on two drugs – Tab. Prazosin (2.5 mg) and Tab. Envas (2.5mg) OD.

DISCUSSION

Atypical HUS is rare and does not have a good prognosis. 33-40% patients die or develop ESRD with first attack of HUS. The treatment options for aHUS are good control of volume status, anemia, hypertension, electrolyte disturbances, peritoneal or hemodialysis, use of Eculizumab, plasma therapy (plasma infusion and/or plasma exchange) and kidney transplant. Eculizumab, a monoclonal humanized anti-C5 antibody, is indicated in first time diagnosed aHUS or already diagnosed and on other modality of treatment. For patients with aHUS who have kidney failure, eculizumab offers them the potential for a kidney transplant and an opportunity to restore their health and have a life free from the restrictions of dialysis and the need for frequent plasma therapy. For patients with active disease, eculizumab offers them the possibility of avoiding end stage renal failure, dialysis and kidney transplantation, as well as other organ damage. Results from the prospective studies showed that, compared with baseline, treatment with eculizumab improved systemic thrombotic microangiopathy activity and led to clinically significant improvements in kidney function and gains in quality of life by 26 weeks[8].

Plasmapheresis (Therapeutic plasma exchange) was initiated as Eculizumab is unavailable in India. The cost of therapy also is very high. We started the plasmapheresis, using the special plasma filter technique[6], with a lower volume to see for patient compliance and then we increased the dose of FFP[7]. Eventhough, the effectiveness of plasmapheresis is not demonstrated in inducing total disease remission, it is still the treatment of choice. It could prevent relapses and preserve the renal function if initiated early and rigorously[6]. It decreases the mortality from 50% to 25%[4]. In a case report by Georgaki-Angelaki H, et al[5]. their patient was initially started with peritoneal dialysis and plasma exchange was performed after six weeks. Post plasmapheresis (seven cycles) the patient started recovering (evidenced by the platelets and LDH levels). Due to complications, plasmapheresis had to be stopped, and the patient was later discharged on CAPD. Plasmapheresis helped in the gradual improvement of their patient. They however could not associate the patients renal function recovery with plasmapheresis. Their patient was found to be negative for anti-factor H autoantibodies. Inspite of this plasmapheresis was found to be beneficial, suggesting its effective role. In another case by Arnaud Lionet, et al[3]. they initiated plasmapheresis with FFP and intermittent hemodialysis and after four days patient showed signs of recovery. Plasmapheresis was stopped but patient became HD dependent. They restarted plasmapheresis. Anti CHF antibody titer was high.(positive) Corticosteroids and rituximab were started, and plasmapheresis gradually stopped, but patient was HD dependent till renal functions returned to normal.

We believe that early initiation of plasmapheresis and the addition of corticosteroids have helped in the favorable outcome in our patient. Hematological remission was complete after plasmapheresis, suggesting that removal of antibodies by plasmapheresis and suppression of formation of new antibodies by steroids may have played a contributory role[2,4,5]. There was no need to add rituximab / cyclophosphamide in our patient. The antihypertensives could be tapered off rapidly as the patients renal function was also normalized. We had not gone in for a renal biopsy to know the extent of renal parenchymal damage, but considering the rapid recovery of our patient, we assume it was minimal.

The final outcome of aHUS is unpredictable and is a matter of concern. It affects the patients quality of life and of the family as well. Our patients recovery suggests the same.

CONCLUSION

Early plasmapheresis contributes to the clinical and biochemical recovery in aHUS, along with cortico-steroids.

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CASE REPORT

MRI FINDINGS IN DENGUE ENCEPHALITIS: A CASE REPORT

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ABSTRACT

Dengue viralinfection is common worldwide associated with high morbidity and mortality. Encephalitis has been well reported and is thought to occur with severe dengue infection leading to liver failure, shock, coagulopathy and leading to cerebral insult. Dengue encephalitis patients usually present with fever, altered sensorium, thrombocytopenia and high antibodytitresat the time of admission.Currently, neurological manifestations related to dengue infections are increasingly being observed. Dengue fever associated with encephalitis has high morbidity and mortality and only few studies have been published regarding Dengue encephalitis. Here, we present MRI findings in a case of Dengue encephalitis focusing on a better understanding of the disease for the clinical practice.

Keywords: Dengue,encephalitis, flavivirus, viral, MRI

CASE HISTORY

A 22 year old pregnant woman at 34 weeks of gestation with viral fever, erythema multiforme and myocarditis who presented with complaints of acute onset weakness in right lower limb and hyper-reflexia. Lab investigations showed thrombocytopenia and dengue positive serology.

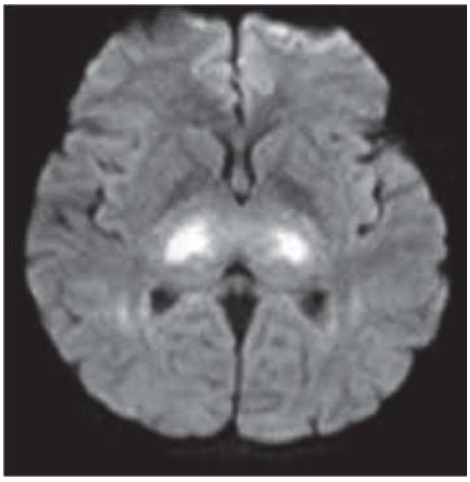

Figure 1: Axial DWI image showing diffusion restriction in bilateral thalami.

MRI with DWI was performed with a 1.5 T scanner. MRI images showedhyperintensity in bilateral thalami, pons and bilateralperirolandicpost central gyri. DWI imagesshowed diffusion restriction in bilateral thalami (Figure 1) and pons (Figure 3).Blooming wasnoted on GRE in bilateral perirolandic post central gyri (Figure 2).

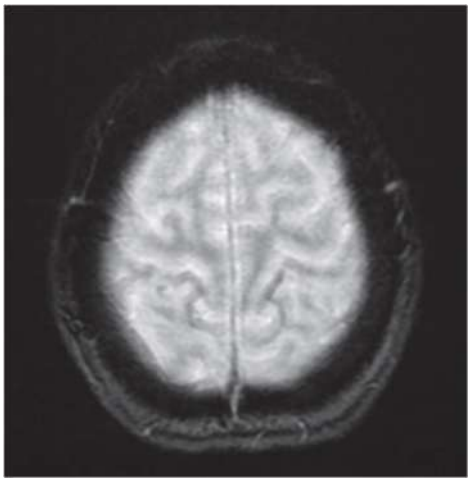

Figure 2: Subtle bilateral perirolandic post-central gyralblooming on GRE

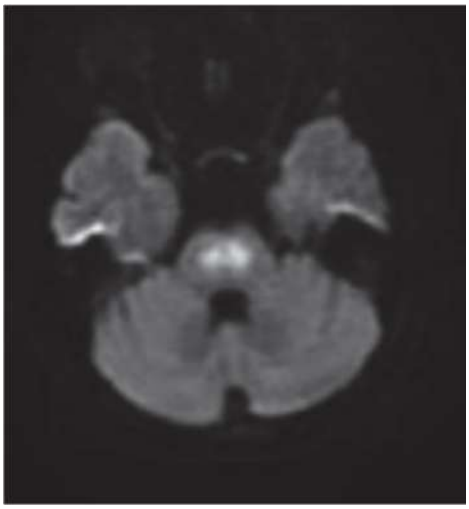

Figure 3: Axial DWI image showing restricted diffusion in pons

DIAGNOSIS: Dengue Encephalitis.

The diagnosis of dengue was confirmed by positive serology for IgM antibodies and NS-1 antigen positivity.

DISCUSSION

Dengue virus is a single-stranded RNA virus belonging to Flaviviridae family.Dengue viral infections are very common in Southeast Asia and all 4 serotypes are found.It is known to cause dengue fever and dengue haemorrhagic fever. Headache, alteration of consciousness, irritability, insomnia, seizures, focal neurological deficits associated with encephalitis, encephlalopathy and stroke pictures are the most common symptoms observed during acute dengue.Encephalitis is a very common neurological complication with dengue fever and is due to direct neuronalinfiltration by the virus. Furthermore, the cases may be underestimated.

Neuropathogenesis of DENV infection is still poorly understood. Viral and host factors may play an important role in the neurological disorders associated with Dengue. In this context, direct viral infection of central nervous infection, autoimmune reaction, metabolic and haemorrhagic disturbances may be involved in the pathogenesis. [1]

MRI is preferred over CT for better visualization of white matter changes and posterior fossa region.It also excludes other differential diagnoses. In acute viral encephalitis, findings include white matter signal intensity changes, cerebral edema which may progress in later stages to infarction, haemorrhage and brain atrophy. MRI findings of Dengue encephalitis are not very well described in literature. Encephalitis features in brain can be seen in globus pallidus, temporal lobes, thalamus, hippocampus, pons and spinal cord.[2,3,4]

The WHOsurveillance shows that global incidence is rising.[5]Numerous neurological manifestations like transverse myelitis,[6] myositis [7]and Guillian-Barre syndrome [8]have been reported.Dengue encephalitis is a well-recognized and common entity with incidence ranging from 0.5 to 6.2%.[7] It may be due to intracranial bleeding due to thrombocytopenia, cerebral hypoperfusion or cerebral edema.[9] Dengue virus and IgM antibody in the CSF has been reported in patients with dengue encephalitis.

On admission, our patient had a diagnosis suggestive of encephalitis with thrombocytopenia, metabolic acidosis, deranged liver functions and dengue positive serology. The MRI findings in our case are not commonly seen in association with dengue fever.Bilateral thalamic involvement with foci of haemorrhageand involvement of the brain stem is very uncommon with dengue. There is only one similar case report byKambleet al., with similar MRI findings.[10]

The outcome in dengue encephalitis depends upon how early the diagnosis is made and managed aggressively in due course of time because we can anticipate the course of encephalitis and its complications. Misra et al, proposed that encephalitis lies in the severe end of the spectrum of dengue infection.

CONCLUSION

Increasing incidence of dengue fever with encephalitis is associated with high morbidity and mortality. Diffusion weighted MRI is more likely to show changesin comparisonto conventional MRI with bilateral thalami showing signal changes commonly. We are presenting this case report to show the extensive involvement of brain by dengue virus.

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CASE REPORT

TETANUS IMMUNOGLOBULIN PROBABLY PRECIPITATED PLEURAL EFFUSION IN A HIV PATIENT

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ABSTRACT

A case report is about the development of tetanus in a HIV+ patient, who is immunized with tetanus toxoid. Later on patient developed pleural effusion. The role of tetanus immunoglobulin in precipitating pleural effusion has been doubted.

Keywords: Tetanus, Pleural Effusion, HIV, ART

INTRODUCTION

Development of tetanus following booster dose of tetanus toxoid in HIV patient is not uncommon. There are reports of tetanus in previously immunized HIV+ patients. Also, Immunoglobulin (I_g) acts as a immunmomodulator, and perhaps immunoglobuln precipitated Pleural effusion.

CASE REPORT

A 30 year old HIV+ male patient, who is getting combination antiretroviral therapy (cART) since June 2011 at ART centre Khagaria, in northern part of India. On 2nd April 2016, Patient attended ART centre because of lockjaw, and mild rise of temperature, which he developed on previous day. Clinical examination revealed lockjaw without any local inflammatory causes and also opisthotonus. Diagnosis of Tetanus was made. Patient had the history of bite by non rabid dog a few months back, and he received booster dose of tetanus toxoid. Patient was treated with 4000 IU of tetanus immunoglobulin IM besides Metronidazole and Diazepam IV. Though patient recovered from tetanus on the 7th day, subsequently he complained of shortness of breath. Total leucocyte count was 11,200/cmm and polymorphs and lymphocytes were 81% and 14% respectively. CD4+ T cell count was 316/cmm. Liver and renal functions were normal. X-ray chest revealed left sided pleural effusion (fig.1). Tuberculin Skin Test and sputum smear for AFB did not contribute to the diagnosis. Even though, It was assumed a case of HIV-Tb. co-infection. Nevirapine in cART was changed to Efavirenz. Simultaneously, DOTs under RNTCP was started. After 25 days, breathlessness subsided, and the X-ray chest showed minimal effusion. Subsidence of pleural effusion following antituberculous treatment confirmed the pleural effusion caused by tuberculosis.

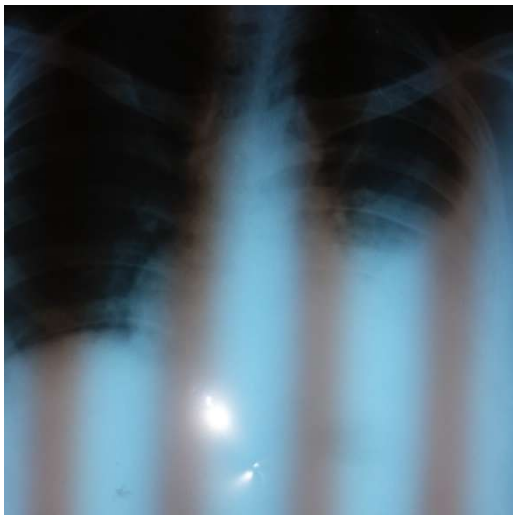

Figure 1: Left sided Pleural Effusion

DISCUSSION

Waning of immunity or subnormal response to booster dose of tetanus toxoid has been seen in immunized patient of HIV[1] due to T-cell dysfunction that happens in patients early in the course of infection, even when the CD4+ T-cell count is in low-normal range. The degree and spectrum of dysfunctions increase as the infection progresses. One of the first abnormalities to be detected is a defect in response to remote recall antigens, such as tetanus toxoid and influenza, at a time when mononuclear cells can still respond normally to mitogenic stimulation[2].Immunoglobulin (Ig) has immunomodulatory effect. High-dose IV Ig is administered routinely as

a treatment of a variety of human inflammatory disorders. Because of anti-TNF-α, also used in some of the same inflammatory disorders, has been shown to cause reactivation of TB. However, immunoglobulin has been shown to have therapeutic effect when given to mouse model of tuberculosis[3].

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CASE REPORT

IMPACT AND BIOMECHANICAL MECHANISMS OF TORTUOSITY OF ABDOMINAL AORTA- A CASE REPORT

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ABSTRACT

Abdominal aorta is the major arterial avenue to supply oxygenated blood to human body.Its luminal diameter,thickness and tortuosity are predisposing factors for variation of blood pressure. We report a case where there is buckling of the abdominal aorta in an elderly female.In the present cadaveric study we have analysed the possible factors that might produce such deformity. The knowledge of anatomic characteristics of abdominal aorta , and early detection by clinical symptoms and radiological diagnosis can prevent catastrophe.

Keywords: Abdominal aorta, tortuosity, aneurysm

INTRODUCTION

Abdominal aorta is the largest elastic artery to provide blood to systemic circulation. The caliber diminishes from above downwards. The cadaveric superior and inferior calibers are between 9-14mm and 8-12 mm respectively [1] .The relation between aortic size and shape is a possible causative factor in the developement of abdominal aortic aneurysm. [1,2]

We report a case where there is buckling of the abdominal aorta in an elderly female.The present study have analysed the possible factors producing such deformity. Knowledge of tortuosity of abdominal aorta with danger of aneurysm and rupture is of immense importance to clinicians and vascular surgeon.

CASE REPORT

Routine abdominal dissection of an elderly female cadaver around 65 yrs age revealed a curved course of the abdominal aorta.At the upper pole of the left kidney the aorta deviated to the left described a sinuous course, turned to the right 2cm below the lower pole of left kidney and continued below to the right side of the midline till its bifurcation into common iliac arteries.As a result,inferior vena cava was further pushed to the right.

The diameter of the abdominal aorta progressively reduced from the point of deviation as shown in the Table 1.The maximum convexity to the right was 2cm below origin of superior mesenteric artery where the wall was found to be thickest. Just before bifurcation into common iliac arteries the wall thickness was minimal.

Table 1: Dimensions of Abdominal Aorta at different levels

Site	Diameter(Cm)
Upper pole of left kidney	7
2cm below origin of SMA	**7.2***
Lower pole of left kidney	5.8
At the origin of IMA	5.5
Just before bifurcation	**5.3****

* Thickest; ** Thinnest

Right hepatic,left hepatic and right gastric arteries arose separately from the common hepatic artery.Splenic artery was found to originate from the superior mesenteric artery.Rest of the ventral branches were according to normal anatomical configuration.Among the lateral branches,left inferior phrenic was a branch of abdominal aorta ,but right inferior phrenic arose from the coeliac trunk.There were two renal arteries on the left side.Upper renal artery arose from the level of origin of superior mesenteric artery(SMA) and entered the hilum.Lower artery arose below the SMA and also entered the hilum separately.Renal artery on the right side was normal in disposition .Both the gonadal arteries were extremely slender and arose below the renal arteries. Great saphenous vein drained into the external iliac vein just below the inguinal ligament on both sides.A cystic lesion was found on the anterior surface of the right kidney.

DISCUSSION

Abdominal aorta is formed by the fusion of the two dorsal aortae in a caudo-cranial fashion.Congenital

narrowing or coarctation of aorta is primarily a defect of the tunica media,followed by proliferation of the tunica intima.Most of the changes in caliber of abdominal aorta occur in later ages and are acquired.Tortuosity may be considered as a geometrical risk factor in the development of the disease.Midline straight vessels like the abdominal aorta, have a tendency to develop tortuosity with increasing age due to loss of longitudinal stiffness. The exact mechanism of development of tortuosity of a blood vessel is not very clear.Carotid artery tortuosity have been shown to be associated with high blood pressure, atherosclerosis, and other diseases.

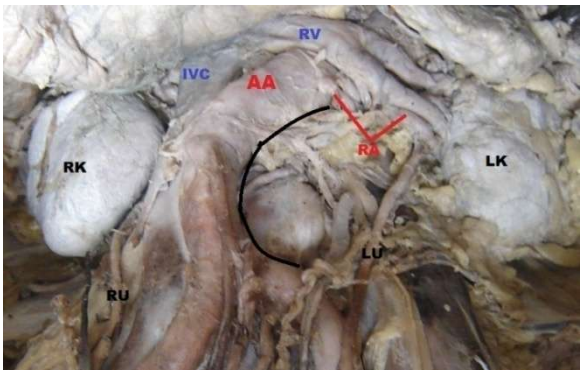

Figure 1: AA- abdominal aorta,IVC- inferior vena cava,RV- left renal vein,RK-right kidney,LK- left kidney,RU-rt ureter,LU- lt ureter,RA- lt lower renal artery,Black curved line- tortuosity of abdominal aorta

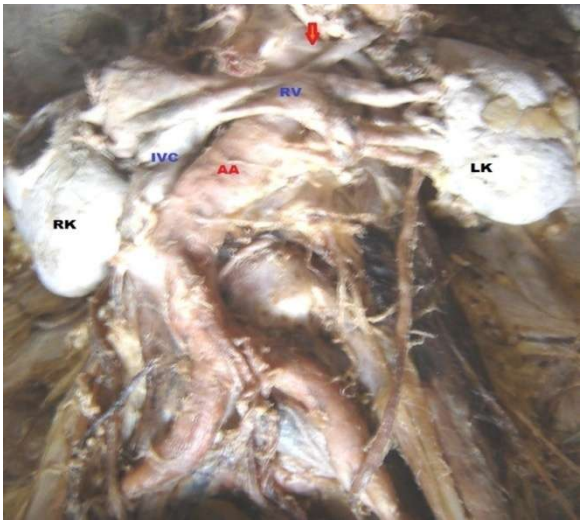

Figure 2: AA-abdominal aorta,IVC- inferior vena cava,RV- left renal vein,RK-right kidney,LK- left kidney, Red arrow – shows upper lt renal artery

Liu Q et al [3] have suggested that arterial buckling could be a possible mechanism for the initiation of tortuous shape. Experimental results showed that under pulsatile pressure arteries buckled when the peak pressures were approximately equal to the critical buckling pressures under static pressure.[3] The stability of blood vessels under the lumen blood pressure is essential to the maintenance of normal arterial function. Han HC[4] demonstrated that arteries may buckle due to high blood pressure or low axial tension and that residual stress in the arteries increases the buckling pressure. At junctions like aortic bifurcation, transmitted pressure waves may weaken the intimal lining. Difference in luminal diameters of common iliac arteries may set up turbulence in blood flow, injuring the the intima of the distal abdominal aorta.[1]

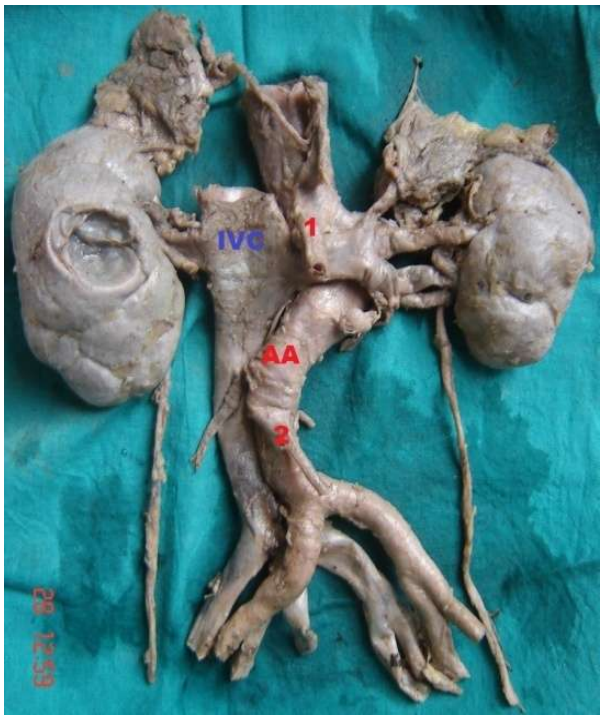

Figure 3: AA-abdominal aorta,IVC- inferior vena cava,1- superior mesenteric artery,2-inferior mesenteric artery

The haemodynamic implications of tortuosity are likely to create flow profile asymmetries as a consequence of which abnormal wall shear stress develops and prones the vessel to atherosclerosis.[5] Aortoiliac tortuosity particularly in the infrarenal region is associated with increased complexity of endovascular aneurysm repair and with predischarge endoleak and more frequent use of arterial reconstruction.[6] In a study by Fillinger MF et al[7] anatomic characteristics of ruptured abdominal aortic aneurysms were studied radiologically. Abdominal aortic diameter of 6.5 ± 2 cm with value of 5.6 cm±1 cm in the control group ($p<.0001$) was significantly associated with rupture abdominal aortic aneurysm. In the present case the tortuosity and diameter of the abdominal aorta had similar predisposing factors for rupture. Mild tortu-

osity may be asymptomatic,but severe tortuosity can lead to ischemic attack in distal organs.

Clinically,tortuous arteries and veins with aging are linked with atherosclerosis, hypertension, genetic defects and diabetes mellitus.[8] Vessel tortuosity causing high fluid shear stress, is a precursor of thrombosis. Thrombus was initiated at inner walls in curved regions due to platelet activation. Initiation of thrombus is hastened due to increased venule tortuosity modifying fluid flow. Compared to the same sized venule, flow in the arteriole generated a higher amount of mural thrombi and platelet activation rate. So, the extent of tortuosity is an important factor in thrombus initiation in microvessels.[9]

Arterial tortuosity syndrome (ATS) is an autosomal recessive connective tissue disorder, mainly characterized by tortuosity and elongation of the large- and medium-sized arteries with predisposition to stenoses and aneurysms. Vascular imaging revealed kinking and anomalous origin of the aortic arch branches, marked tortuosity of the aorta, pulmonary and most middle arteries, and a small aneurysm of the splenic artery.[10]

So tortuosity ,alteration in caliber of major blood vessels like abdominal aorta are essential risk factors for development of atherosclerosis,thrombus formation, rupture and other fatal complications.The knowledge of anatomic characteristics of abdominal aorta ,lumen diameter and early radiological diagnosis can prevent catastrophe.

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CASE REPORT

RADIOTHERAPY FOR PIGMENTED VILLONODULAR SYNOVITIS: A CASE REPORT

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ABSTRACT

This is a case report of a 13 year old boy who has been operated for Pigmented Villonodular Synovitis (PVNS) and treated with adjuvant post-operative radiotherapy for incomplete surgical resection. This report mainly highlights the role of radiotherapy in managing this rare benign condition with emphasis on improving local control rates with functional joint preservation and avoiding repeated surgeries.

Keywords: Radiotherapy, PVNS (Pigmented Villonodular Synovitis), Surgery

INTRODUCTION

Pigmented villonodular synovitis (PVNS) is a rare proliferative disorder of the synovium affecting any joint but frequently found in the knee. PVNS is an extremely rare condition affecting only 1.8 people per million.[1] Therefore, treatment data are relatively sparse, especially concerning the use of radiotherapy or other modalities (RT).

CASE REPORT

A 13 year old boy with no significant past medical history presented witha history of, gradually increasing left knee joint swelling since last 7 year. It was also associated with on & off pain withlimitation of left knee joint movements. He denied any history of major trauma. He was evaluated for the same by orthopedic surgeon and diagnosed with diffuse PVNS after MRI of left knee joint. He underwent arthroscopic synovial biopsy plus total synovectomy of left knee in June 2015.The histopathology was reported as Pigmented Villonodular Synovitis (PVNS). The postoperative MRI of left knee showed minimal residual disease in the peri-articular region, posteriorly. He was referred to Oncology Department for postoperative radiotherapy. He was treated with External Beam Radiotherapy (EBRT) with cobalt machine (^{60}Co-γ rays) with antero-posterior opposed fields to a total dose of 36 Gy in 18 fractions. He tolerated the treatment wellwithout any side effects during the course of radiotherapy. The patient also attended school on daily basis during the EBRT schedule. He completed treatment on 5th October, 2015. The patient was on regular follow up since then at our institute. As per the case record the follow up MRI was done on 16th April2016 which showedvery good regression of lesion compared to previous MRI dated Jun 2015. However, mild synovial effusion and irregularity of Hoffa's fat pad is seen in the scan. Clinical examination revealed mild restriction in flexion movement. Clinically there is no significant joint pain or swelling with almost normal joint activity. He is advised to attend clinic regularlyfor follow up and necessary evaluation.

DISCUSSION

In 1941, Jaffe et al defined pigmented villonodular synovitis (PVNS), bursitis, and tenosynovitis as yellow-brown villous or nodular, tumor like lesions containing closely-compacted polyhedral cells, multinuclear giant cells, lipoid cells and hemosiderin-containing cells. It is known to be a benign proliferative disorder of the synovium.Lesions can be classified into localized and diffuse forms. The localized form is often effectively treated with local excision. In contrast, diffuse PVNS is typified by widespread involvement of the synovium with villous and coarse nodular outgrowths.

Diffuse PVNS is usually treated with total or near total synovectomy and have a much higher rate of recurrence, often requiring multiple surgeries and additional therapy.The goals of surgery for patients with diffuse intra-articular PVNS are to restore function of the joint and to prevent the destruction of articular cartilage by completely resecting the diseased synovium. Although, the treatment of choice is surgical excision, complete resection may be difficult depending upon the area to be resected (partial versus complete synovectomy) and the joint in-

volved.Local control rate for surgery alone varies from 44-92%.[2] Postoperative radiation can improve the local control rate (more than 90%).Radiation therapy may be used as the primary treatment modality for diffuse intra-articular PVNS, but it is considered to be better option for postoperative cases with total or incomplete resection. Radiation can be administered either by external beam radiotherapy (EBRT) or through intra-articular injection of radioactive isotopes also known as radiosynoviorthesis.[3,4]Intra-articular injection of a radioactive isotope uses several β-emitting isotopes which are colloid molecules bound to a bulky molecule to minimize resorption and leakage. But due to the cost of drug, availability and need for invasive procedures to inject the drug into the joint space, EBRT has been used widely as an easier and cheaper approach.

External beam irradiation is usually employed after the incomplete resection of disease. Radiation doses ranging from 20 Gy to 50 Gy are administered in 15–25 fractions, beginning about 6–8 weeks following surgery.[4]The optimal dose and fractionation schedule of radiation for PVNS is unclear. Some have reported using doses as low as 16 – 20 Gy without recurrence, whereas others have used doses as high as 50 Gy without complications. Myers et al recommended a dose of 36 Gy with conventional fractionation.[1]

Positive surgical margin, history of previous surgery and joint location are the reported factors that increase the likelihood of recurrence.[5,7]PVNS recurs more frequently in the knee, owing to the large capacity of the joint and the difficulty in performing a true total synovectomy. The final pathway of PVNS of knee is total joint destruction leading to joint replacement. Incomplete synovectomy leads to higher recurrence rates and same has been reported in literature.[8,9](56% and 50%, compared with those for complete resection 7% and 20%, respectively). Addition of radiotherapy can minimize these recurrences with less need for repeat surgery. Postoperative external beam radiotherapy has surely shown to minimize recurrence rates in young healthy individuals. Blanco and colleagues reported 14% recurrence rate for patients who underwent external beam irradiation after partial synovectomy, a rate that was comparable to the recurrence rate for patients who underwent total synovectomy for diffuse intra-articular PVNS.[10]In our case the patient had a diffuse type PNSV with incomplete surgical excision. So the decision was taken to treat with postoperative radiotherapy considering the young age and functional preservation of joint activity.

CONCLUSION

Pigmented villonodular synovitis is a rare benign proliferative disorder of the joints. Local recurrence rates are common after surgery especially in cases with incomplete resections. Postoperative adjuvant external radiotherapy is safe and effective adjuvant modality to improve the local control rates with reduction in repeated surgical procedure and maintaining functional joint capacity.

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CASE REPORT

PRIMARY NASOPHARYNGEAL TUBERCULOSIS: A RARE CASE PRESENTATION

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ABSTRACT

Primary nasopharyngeal tuberculosis (TB) is extremely rare. However, in endemic areas, isolated nasopharyngeal TB may present mimicking a malignancy. We report here a case of 31-year old male who presented with multiple lymphadenopathis in the neck. Furthermore, North Eastern part of the country has a high incidence of nasopharyngeal cancers. The diagnosis of primary nasopharyngeal TB was confirmed by histopathology of the nasopharyngeal lesion and negative finding on chest imaging.

Keywords: Malignancy, nasopharynx, primary, tuberculosis

INTRODUCTION

Tuberculosis [TB] is one of the most common granulomatous infectious diseases in India. It can affect any organ in the body, although it has high predilection for pulmonary infection but otorhinolaryngological TB constitutes less than 5% of all cases of extra-pulmonary TB.[1]The North East (NE) part of India is an endemic region of nasopharyngeal cancer.[2] TB of nasopharynx may be primary variant without pulmonary involvement. Description of nasopharyngeal tuberculosis is very limited in the literature.

CASE REPORT

A 31-year old male patient presented with the chief complaint of multiple neck swellings on left side ofthe neckof 2 months duration. There were no histories of nasal bleed, nasal obstruction, snoring, repeated upper respitatory tract infections or decreased hearing. His preliminary Ear Nose and Throat examination showed a mass in the roof of nasopharynx on posterior rhinoscopic examination. On the neck there weretwo nodes in Level-II and Level V. The nodes were firm, mobile, non tender and the maximum size of the lymph node measured 3cm. Further examination by nasal endoscopy showed a smooth surfaced congested growth in the superior wall of nasopharynx, which was compressing the opening of the torus tubaris on right side and it bled easily on touch.His contrast enhanced computer tomography (CT) of nasopharynx and neck showed a growth in the nasopharynx with multiple neck nodes (Figure 1). A biopsy was taken from the nasopharyngeal growth and sent for histopathological examination.

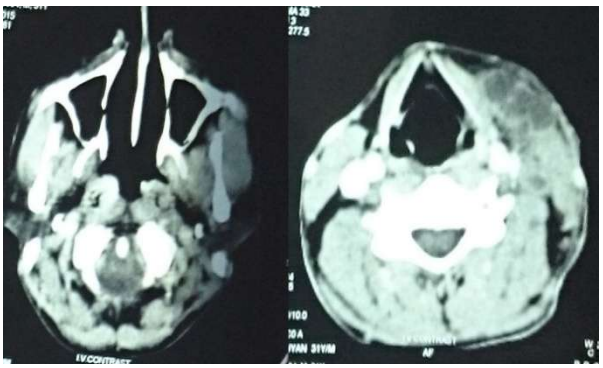

Figure 1: CT scan shows asymmetric soft tissue thickening involving the posterolateral aspects with effacement of fossa of Rosenmuller with bilateral multiple partially necrotic nodes

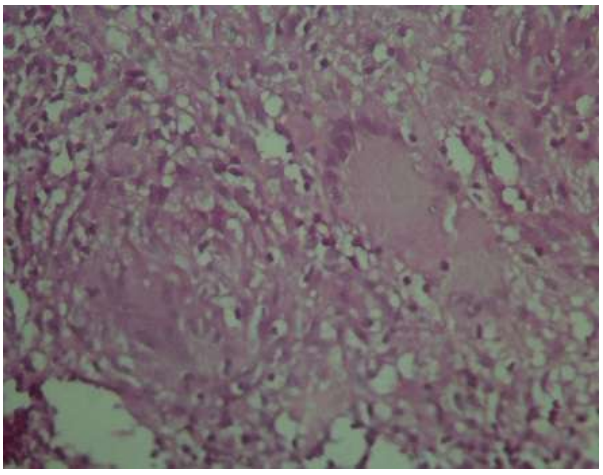

Figure 2: Photograph with H&E stain (40X) showed fragments of respiratory epithelium with underlying lymphoid tissue showing epitheloid granuloma suspecting Koch's

It showed features of granulomatous disease suggestive of tuberculosis (Figure 2). Fine needle aspiration cytology (FNAC) was inconclusive. Wedge biopsy of the node in Level V was performed which showed features of necrotizing, granulomatous lymphedinitits suggestive of Koch's lymphadenopathy.

Imagining for the primary locus and other loci were done. High resolution CT of the thorax showed no pulmonary lesion and ultrasonography abdomen was normal. The diagnosis of primary nasopharyngeal TB with tubercular lymphadenopathy was confirmed. The patient was further referred for the treatment of TB.

DISCUSSION

In the NE India nasopharyngeal cancer and TB are not so uncommon. Isolated nasopharyngeal tuberculosis is a very uncommon presentation even in very tuberculosis prevalent area like India. Primary nasopharyngeal involvement probably occurs due to reactivation of dormant acid fast bacilli in the adenoids or due to direct mucosal infection after inhalation of the bacilli,[3]or contact with the lung secretions the infection spreads to the nasopharynx. Nasopharyngeal tuberculosis appears in 1.9% of patients with pulmonary tuberculosis. However, primary nasopharyngeal tuberculosis without the lung involvement is very rare. According to Rohwedder et al and only 0.1% nasopharyngeal involvement were detected in primary active pulmonary tuberculosis patients.[4] Clinical presentation and imaging studies also present a challenge for the clinician and otolaryngologists to diagnose a isolated nasopharyngeal TB.[5]Coming to the diagnostic part the history and clinical presentation was highly suggestive of nasopharyngeal carcinoma, and the clinical picture resembles the classical case of nasopharyngeal carcinoma. CT scan commonly shows either diffuse mucosal thickening or a moderately enhancing polypoidal mass in the roof of the nasopharynx, which may be ulcerated.[6] MRI commonly shows a mass or diffuse mucosal thickening of intermediate signal intensity on T1W and T2W sequences, with moderate contrast enhancement on T1W images.[7]Our CT scan shows the mass in the posterolateral wall with effacement of the fossa of Rosenmuller which was in favour of nasopharyngeal carcinoma, but the distinguishing features were, no extension of the growth in to adjacent structures, no contrast enhancement andno bony decalcifications of skull base.The other diagnostic difficulty is the similar histopathological for both the nasopharyngeal carcinoma and primary tuberculosis of nasopharynx.[5] In our case the typical features of TB like epithelial granuloma was present which was diagnostic. In addition, to rule out any coexisting malignancy like lymphoma, we had done biopsy from the neck node.

CONCLUSION

In endemic areas high degree of suspicion for Koch's in nasopharyngeal mass should be raised despite features that may suggest malignancy. Primary nasopharyngeal tuberculosis is extremely rare and it may mimic a malignancy. Complete clinical, radiological and histopathological examinations are required to confirm the diagnosis of TB instead of a malignancy.

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test tool. Out of the total 3304 subjects, 45.5% i.e. 1502 were having 4 or more risk factors present. Total of 548 males (46.5% subjects) had high score of risk factors. Females were also nearly in same proportion (44.9%).This was however not statistically significant.

Table 5: Prevalence of Chronic Kidney Disease among various age groups (at risk)

Age	CKD prevalence
40-49 yrs	0%
50-59 yrs	1.10%
60-69 yrs	5.10%
70-80 yrs	8.20%

($\chi_{(3)}^2 = 112.516$; $p < 0.0001$)

Table 3 shows the prevalence of chronic kidney disease. Out of the total survey population i.e. 3304, 2.1% (68 subjects) of the population were found to have CKD. Among the subjects who were at risk according to the SCORED screening test tool, about 4.5% subjects had CKD.

Table 4 shows the prevalence of CKD, according to gender, in the population who is at risk (According to SCORED test tool). Among at risk population, more females (4.7%) were found to have CKD as compared to 4.2% of the males.

Table 5 shows that the advancing age having direct relation with CKD. No case of CKD was diagnosed in the 40-49yr age group. Maximum cases (8.2%) were in 70-80yr age group followed by 5.1% in 60-69 year age group and 1.1% of the subjects in 50-59yr age group. This was highly significant statistically.

DISCUSSION

Global studies have revealed that the emergence of chronic kidney disease as a silent pandemic. CKD usually gets unnoticed as the symptoms appear late when enough damage has already occurred. This study explores the prevalence of CKD and its risk factors using the data from urban areas of Dehradun.

The current study showed overall 2.1% prevalence of chronic kidney disease (2% males and 2.2%females). A similar study by Agarwal *et al* studied south Delhi in 2005 in urban population and reported stage 3 prevalence of 0.785%.[4] The prevalence was low because the cut off for serum creatinine was very high (more than 1.8 mg/dL). Study by Narinder P Singh et al in Delhi (2005-07) on the basis of proteinuria and reduced eGFR reported the prevalence of stage 3 CKD to be 4.2%.[5]

In our study prevalence of CKD was nearly equal in males and females (2% in males and 2.2% in females). Singh in a study in Delhi also showed that there was no difference in prevalence of CKD on the basis of gender.[5] However beyond 60 years of age, females had higher prevalence (5.76% vs. 3.46%).

This study showed the trend of increasing prevalence of CKD with the advancing age. Prevalence among the at risk subjects of the age group 50-59 was 1%; 60-69 year age group was 5.1% and 70-80 year age group was 7.6%. The SEEK-India cohort study also showed higher prevalence in the older age group.[6] Venkatachalam J in Tamil Nadu showed that prevalence of CKD in the age group 60 years and above was 19.8% against the overall 12.3%.[3] Narinder Singh in his study in Delhi found that the prevalence of CKD was increasing with age.[5]

CONCLUSION AND RECOMMENDATIONS

Changes in the lifestyle and habits of urban population lead to increase in prevalence of the risk factors for NCDs. Further, these make a major contribution to association with chronic kidney disease. The cost of treatment is very high for CKD. Thus a healthy lifestyle needs to be adopted to prevent CKD. Specific prevention strategies which reduce exposure to risk factors should be applied. Physical activity plays a major role in preventing chronic kidney disease. Advice should be given for healthy home available diet with low consumption of fat, salt and sugar and more consumption of fresh fruits, vegetables, and dietary fiber etc.

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