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EDITORIAL

Liquid Biopsy – The Non-invasive Tool for Tracking Cancer

Saeeda Baig and Osama Jafarey

Tissue biopsy has been the standard for diagnosis and prognosis of a suspicious lump in a patient since the 11th century.[1] Although tissue biopsy is a standard technique for cancer diagnosis, typing, treatment, and identifying genetic clues for tailor-made strategy of a personalised treatment. However, it is invasive, painful, expensive, and risky which makes serial biopsies simply unfeasible. Sometimes tumors are not accessible; at other times, either solid tumor sample is too invasive, or the tumor heterogeneity prevents genotyping of the sample; or the patient is in critical condition and biopsy cannot be done. These limitations can cause unnecessary delays in the treatment for a disease where time matters seriously. In developing countries, like Pakistan, tissue biopsy encounters inherent difficulties, clinical risks, potential surgical complications, discomfort; and above all, economic considerations.

Liquid biopsy, an alternate to tissue biopsies, is the analysis of tumor degraded material-molecules and cells shed by tumor that are found in various body fluids, including blood, urine, cerebrospinal fluid, or saliva. The collection of these fluids provides minimally invasive, easily accessible and more conveniently repeatable method than a tissue biopsy. *Debris* of degraded tumor cells is released into the blood, and these fragments of tumor DNA (ctDNA), cell-free RNA (cfRNA), circulating tumor cells (CTC), and proteins can be a gold mine for the prediction of potential tests for mutations and future treatment measures. The easily taken multiple and non-invasive sample collection will help monitor tumor progression, keeping track of mutations and response to treatment.[2]

The cancer by-products currently required for liquid biopsy, which are easily accessible in peripheral blood, include CTC, ctDNA, and cfRNA.[3]

Fragments of tumor DNA (ctDNA):

The source of circulating ctDNA is possible cell death whether apoptosis or necrosis. Normally, phagocytosis clears this *debris*. However, in case of malignancies this system is impaired and this increases the circulating DNA levels. CTC could also be a potential source of ctDNA, but discrepancy between number of CTCs and concentration of plasmatic ctDNA suggests otherwise. There are several benefits of using ctDNA. It corresponds to a real-time biomarker and can be used to diagnose and monitor the tumor. Moreover, it can be very useful in solid tumor where collecting a sample is too invasive, or tumor heterogeneity is present or if there is not enough sample to genotype. Multiple samples can be easily collected if required, to monitor tumor progression, monitor response to cancer treatment, enable tracking of mutation in tumor by regularly testing ctDNA, facilitating testing of a new type of therapeuric agent due to quick response to test, and surveillance for relapse in post treatment patients after successful treatment of cancer.[4]

Cell-free RNA (cfRNA):

A highly heterogeneous variety of cells of approximately 30-120 nm in diameter are released into the biological fluids (e.g., blood, urine, bile, or ascites), which are small membrane-enclosed vesicles known as exosomes.[5] These are actively released into the extracellular space containing nuclear material including mRNAs, microRNAs (miRNAs), and other non-coding RNAs as well as cell-specific proteins. Different reports suggest exosomes can be used by cells to shuttle various signals toward neighbouring or distant cells altering both physiological and pathological processes,[6,7] even reprogramming the adjacent healthy cells into facilitated malignant progression.[7] cfRNA can be a novel diagnostic tool in human malignancies in solid tumors, heart injury.[8]

Circulating tumor cells (CTC):

Phenotypic transition of epithelial tumor cells to mesenchymal characteristics permits the tumor-initiating cells to invade the basement membrane of tissue of origin. These cells of the tumor slough off around the edges and escape into the lymphatics or circulation. These are called circulating tumor cells (CTCs), which are roughly 5 CTCs/ml of blood, which lodge and spread in new tissues to form metastases.[9,10] These CTCs are basically the blueprint of tumor composition, invasiveness, drug susceptibility, and resistance to therapy.

Metastatic spread is considered a slow process. However; most cancer deaths occur due to malignant cells spreading and seeding in the other organs of the body. Although an estimated cells per gram of tumor tissue released daily to the bloodstream is about one million, yet a very small fraction develops independent distant tumor. The role of CTC as markers has been researched by number of investigators to foresee the

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progress in different kinds of cancer evaluating recurrence, survival, or response to therapy. Major technological developments have been made to improve CTC detection and isolation rates, using CTC size, physical properties, or specific cell markers. The first FDA-cleared test to capture and enumerate CTC relied on a set of surface markers (CD45-, EpCAM+, CK8+, CK18+). Indeed, antibody-coated magnetic beads targeting EpCAM is the most widely used technique to detect CTC.

Researchers, both from academic and industry, are working on many fronts to develop and establish use of liquid biopsy tests. This research has a huge scope in developing countries where its expansion will have diverse utility area and will help refine and establish clinical uses generating an entirely new field of low cost therapy.

There are certain shortcomings or constraints of these techniques reported by some studies, which add a layer of complexity to the challenges of recognising and identifying multiple biomarkers for various cancer types.

In 15 percent of the patients, tumors are localised and do not shed DNA into circulation at detectable levels. A huge variation in DNA mutations occurs between patients suffering from same type of cancer. Some mutations may be similar among many patients with one type of cancers; but on the other hand, some may not be there altogether. Sometimes, ctDNA may be released from certain parts of tumor and not the whole tumor. It is also not known that mutations discovered are those which do not control tumor growth or those that control the cancer's biology. These limitations are insignificant compared to the huge benefits that humanity will achieve.

The scenario in Pakistan regarding cancer is very limited. Since last 64 years, no population-based study for accurate nationwide cancer incidence has been conducted; and hence, no figure is available. However, as per calculation of WHO which is two new cancer patients/year/1000 of population, it can be estimated to be 0.4 million new cancer patients in a population of 200 million.[11] To cope with these huge numbers, we need to be abreast with new techniques to overcome fundamental complexity and financial constraints of our region. These can be researched with minimum resources and many such projects can be simply developed in our setting. The techniques involved in this development are not complicated and can be explored in developing countries, like Pakistan.

The discarded molecules of tumors and cells, which scientists discovered more than 100 years ago, are a treasure that can take care of unachievable ventures in cancer treatment. It can be a real-time easy assessable diagnostic or prognostic tool for days to come in comparison to other standard methods. A liquid biopsy test could be used as a routine pre-screening method in healthy individuals to identify those who may have early-stage cancer and are candidates for other (possibly more costly or invasive) screening tests after due testing.

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ORIGINAL ARTICLE

Quantitative Analysis of the Area of the Apical Ectodermal Ridge in Chick Appendages Using Image-J

Hamd Binte Shahab Syed[1] and Muhammad Yunus Khan[2]

ABSTRACT

Objective: To determine the effect of sodium phenytoin on the apical ectodermal ridges (AER) of chick wing buds by using the software program Image-J.

Study Design: An experimental study.

Place and Duration of Study: Department of Anatomy, Regional Center, College of Physicians and Surgeons Pakistan (CPSP), Islamabad, from January 2014 to January 2015.

Methodology: Sixty fertilised chicken eggs of '*Egyptian fayoumi*' breed were selected and separated into experimental (B) and control (A) groups, each having 30 eggs. A single dose of 3.5 mg sodium phenytoin was injected into each egg of the experimental group. The controls were injected with the same volume of normal saline. Developing embryos were extracted 96 hours (day 4) after incubation and histological sections were cut at 5 μm thickness. These sections were stained with Feulgen Nuclear and Light Green. The area of apical ectodermal ridges of chick wing buds was calculated by employing Image-J and subjected to statistical analysis.

Results: The difference between the mean values of the area of apical ectodermal ridges of experimental and control groups, as calculated by Image-J, was found to be statistically insignificant.

Conclusion: Change in the area of the apical ectodermal ridges in experimental chicks, following phenytoin exposure, was insignificant as proven on the basis of quantification by Image-J.

Key Words: *Apical ectodermal ridge. Chick embryo. Sodium phenytoin. Image-J.*

INTRODUCTION

Babies, born to mothers who are administered antiepileptic medication phenytoin throughout pregnancy, are at an increased risk for developing the well-documented fetal hydantoin syndrome. Birth defect of the appendages is a salient feature of the syndrome. This includes digital hypoplasia, polydactyly, syndactyly, absent palmar creases, and positional limb defects like club feet.[1,2]

Evidence regarding the exact mechanism of phenytoin-mediated limb teratogenicity is still inconclusive. Several hypotheses have been proposed including gene alterations, ischemic-hypoxic damage, apoptosis and folate deficiency, but the results are uncertain.[3]

Experimental studies on chick embryos have shown that retinoic acid is essential for the initiation of limb outgrowth.[4,5] Phenytoin causes an altered expression of genes involved in key morphogenetic events of embryological development including the retinoic acid receptor (RAR) isoforms. Disturbed retinoid metabolism can influence the normal development of the apical ectodermal ridge (AER), which is the thickened epithelium lining the outer edge of the emerging limb bud.

The AER secretes a variety of molecules involved in signalling processes for limb development. It guides patterning of limb development in the proximo-distal axis. The AER is also involved along with other molecules in interdependent cycles and chains of events for limb development in apico-posterior as well as dorso-ventral axes.[6-8]

Although the apical ectodermal ridge has been a popular model for research in the field of developmental anatomy, data representing measurement of the area of the apical ectodermal ridge by employment of Image-J is scarce. Image-J is a public domain, Java-based image processing software developed at National Institutes of Health (USA).[9] This software provides an effective means to calculate the area of a user's defined image selections. It holds the advantage of being user friendly and can be run easily on any computer system. Image-J has been effectively used in both national and international research for the measurement of histological parameters.[10,11]

The objective of this study was to determine the effect of sodium phenytoin on the apical ectodermal ridges (AER) of chick wing buds by using the software programme Image-J.

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METHODOLOGY

This was an experimental control study carried out in the research laboratory located in the Department of Anatomy at the Regional Centre of College of Physicians and Surgeons Pakistan (CPSP), Islamabad.

Sixty freshly laid fertilised chicken eggs belonging to '*Egyptian Fayoumi*' breed were obtained from the Poultry Research Institute (Rawalpindi). Damaged and dirty eggs were not included. The eggs were chosen on the basis of the random selection technique. The eggs were divided into two groups A and B having thirty eggs each. Group B was the experimental group and each egg in this group was injected with 3.5 mg of sodium phenytoin. Group A was the control group and each egg in this group was injected with an equivalent volume of normal saline.

The teratogenic dose 3.5 mg of sodium phenytoin per egg was selected as the dose for injection in the experimental embryos for this study.[12]

In the chick embryo, at 96 hours (day 4) of development, the apical ectodermal ridge reaches a maximum thickness and height, after which it regresses. Therefore, in this study, duration of exposure to the drug was 4 days.[13]

Before injection, the eggs were wiped clean with a swab soaked in 70% alcohol, and placed vertically in the egg rack with the broader end facing upward for ten minutes. During this time, the blastoderm in the eggs floated upward to settle just beneath the air sac, so the drug could be injected safely into the lower pointed end of the eggs without risk of damage to the blastoderm. Using a thumbpin, two holes were drilled into each egg, one at the broad upper end and the other just a fingerbreadth above the pointed lower end. The reason for drilling a hole at the upper end was to allow air to escape, creating a space for entry of the drug at the lower end. The drug or normal saline was injected into each egg with the help of an insulin syringe (needle length 8 mm, 30 gauge) directly into egg albumen.[14] The holes were sealed with melted paraffin and transferred to the incubator and this was noted as day 0 of development. Temperature in the incubator was kept at 38 ±0.5°C and relative humidity was maintained between 60 to 70%. The eggs were rotated ½ turn twice daily for uniform distribution of heat.

On day 4 (96 hours) of development, the eggs were taken out of the incubator and placed horizontally on a flat table for ten minutes, allowing the blastoderm to float upward above the yolk sac and lie beneath the shell cap. The shell cap of each egg was removed carefully with the help of delicate instruments in a bowl of warm normal saline, exposing the embryo.[15] The embryos were assigned serial numbers and transferred to a Petri dish.

The extracted embryos were fixed in 10% neutral buffered formalin and then processed according to a standardised regimen.[16] Next, they were vertically embedded in paraffin with the head facing downward. Serial sections of 5 µm thickness were cut on a microtome in the dorso-ventral plane to locate the wing buds. The sections containing wing buds were stained with Feulgen Nuclear stain and counterstained with Light Green.[16] Then, these sections were mounted on slides in the synthetic resin Distyrene Plasticizer Xylene (DPX) to be studied under the light microscope.[16]

The apical ectodermal ridge (AER) was identified under oil immersion lens (100 X objective) fitted with the linear micrometer in the eyepiece. This ocular micrometer was calibrated, using a stage micrometer. The maximum ectodermal thickness (height) was measured using the linear micrometer along a line which passed through the thickest portion of the apical ectoderm (including periderm) and it was normal to the line tangential to the base of the ectoderm. The area of the AER was measured in the selected sections with maximum ridge thickness.

Photographic image of each section of maximum ridge thickness was captured through the eyepiece with ocular micrometer fitted in it under oil immersion lens (100 X objective). These pictures were uploaded in the computer. The pictures thus showed the image of scale superimposed on the image of the section (Figure 1).

These photographs were opened in the Java-based software Image-J, and a line was drawn parallel to the scale, superimposed on the picture. Number of divisions covered by this line on the scale were noted and converted into micrometres. The scale was set in the software by feeding the exact calibrated distance thus measured. The free hand tool was employed to outline the exact boundary of the AER. The number of pixels embodied within the marked contours on each section

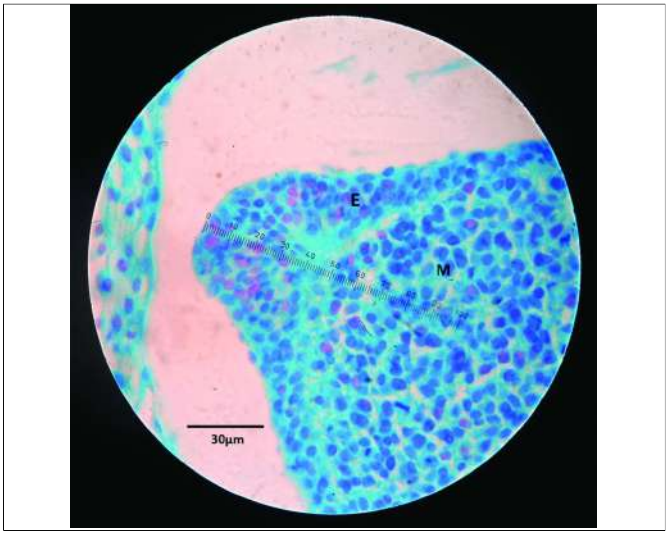

Figure 1: High power photomicrograph showing the apical ectodermal ridge of 96 hours old chick embryo belonging to experimental group (B) with superimposed scale. Mesoderm (M), Ectoderm (E), Feulgen Nuclear and Light Green staining. (Scale bar = 30 µm).

was determined automatically by the software which then calculated the cross-sectional area of the AER from one embryo at a time, which was noted serially in the observation sheet.

The therapeutic dose of sodium phenytoin in humans is 5-7 mg/kg.[17,18] Taking 6 mg/kg as the average dose in humans, the equivalent in one chicken egg was calculated to be 0.3 mg (0.3/50x1000). The average weight of one chicken egg is 50 grams. But previously conducted experiments have failed to produce any significant teratogenicity in chicks after giving 0.3 mg per egg.[19] The teratogenic dose of sodium phenytoin, after conducting a series of preliminary experiments, was found to be 3.5 mg per chicken egg.

All the data were analysed by the Statistical Package for Social Sciences (SPSS) computer software programme (version 16). The area of the apical ectodermal ridge was analysed by applying t-test for the detection of any significant differences between the means of experimental and control groups. The resulting data was expressed as mean ± SD (standard deviation). A p-value of $\leq$0.05 was considered as significant.

RESULTS

The histological picture of the wing buds of experimental chicks resembled that of the controls. The AER was clearly visible with a distinct ectodermal-mesodermal interface. All the specimens showed prominently stained cells (Figure 1).

The maximum thickness of AER in the experimental group had a mean value ± SD of 31.96 ±7.828 μm, which was slightly lower than the control group but the difference of mean values was not statistically significant (Table I).

Table I: Comparison of histological parameters between experimental and control groups.

Parameter	Group B (Mean ± SD) n=30	Group A (Mean ± SD) n=30	p-value
Maximum thickness of AER (μm) n=30	31.96 ±7.828	33.296 ±9.063	0.573
Area of AER (mm² x 10-4) n=30	1.619 ±0.259	1.714 ±0.289	0.218

SD = Standard deviation.

The area of AER in the experimental group had a mean value ± SD of 1.619 ±0.259 mm² x 10-4, as calculated by Image-J. This value was slightly lower as compared to control group. The difference between mean values was statistically insignificant (Table I).

DISCUSSION

In Pakistan, nearly 50% patients prescribed antiepileptic medications are females.[20] The administration of phenytoin in pregnant women with seizures and related illnesses is justified, if the therapeutic benefits outweigh the potential risks, according to FDA (United States Food and Drug Administration).[21]

Keeping this in mind, any research aimed towards developing a better understanding of the possible mechanism underlying phenytoin teratogenicity is of the utmost importance. Transplantation studies, conducted on chick limb buds during various stages of development, demonstrate the key role of the AER in growth and patterning of the limb bud.[22] Research carried out on developing chick appendages have reinforced the inductive role of the AER in limb formation.[23] Any discrepancies in the dimensions of the AER could lead to gross birth defects of the limbs. The AER might be a potential target site for the teratogenic activity of sodium phenytoin.

Using Image-J, a practical method was devised to calculate the dimensions of the AER after prenatal administration of sodium phenytoin in chick embryos. The results of this study showed statistically insignificant difference between the area of apical ectodermal ridges of experimental and control chick wing buds. This shows that phenytoin does not disrupt the normal height/ thickness or area of the AER.

Further research could be carried out to explore any significant changes in the ultrastructural features of the AER after prenatal phenytoin exposure. During this study, Image-J was found to be an objective, cost-effective, reproducible and time-saving method of quantifying the area of the AER. It can be employed similarly in the measurement of other histological parameters during embryological development.

CONCLUSION

Quantitative analysis with Image-J shows that prenatal exposure to sodium phenytoin does not result in any significant change in the area of the apical ectodermal ridges in experimental chick embryos.

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ORIGINAL ARTICLE

Analysis of the Factors Related to the Blood Pressure Control in Hypertension

Fatih Atik, Gulali Aktas, Mehmet Zahid Kocak, Edip Erkus and Haluk Savli

ABSTRACT

Objective: To determine the factors associated with blood pressure control and comparing anthropometric and clinical parameters of subjects with well-controlled hypertension to those with poorly controlled blood pressure.
Study Design: Observational cross-sectional study.
Place and Duration of Study: Abant Izzet Baysal University Hospital, Bolu, Turkey, from January to June 2016.
Methodology: Medical data obtained and recorded from computerised database and case files of our clinic. Subjects with mean blood pressure above target levels were defined as poorly controlled and others were as well-controlled hypertension group according to JNC VIII.
Results: Out of 342 subjects, only 116 (33.9%) were aware of normal blood pressure range. The number of patients who had a blood pressure on goal in the group and knew the normal range of blood pressure was significantly higher than the patients in group who did not know the normal range of blood pressure. Body mass index and waist circumference were both significantly higher in poorly controlled compared to well-controlled hypertensive subjects. Treatment compliance was significantly associated with better control of hypertension.
Conclusion: Striking results of present study indicate that lower body mass index and lesser waist circumference along with treatment compliance and awareness of normal blood pressure ranges are important factors that affect reaching treatment targets in hypertensive subjects.

Key Words: *Hypertension. Blood pressure. Treatment compliance. Body mass index. Waist circumference.*

INTRODUCTION

Hypertension (HT) is one of the most important health issues that affects approximately 30-40% of the adult population in developed countries.[1] Around one billion people suffer from HT. It is considered as a modifiable risk factor for myocardial infarction, stroke, heart failure, atrial fibrillation, aortic dissection, and peripheral arterial diseases.[2] The main target of antihypertensive treatment is reducing the morbidity and mortality from cardio-vascular and renal complications of hypertension.

Although there are effective treatment options for hypertension, awareness and control rate of the disease is still low. Only half of the patients are aware of hypertension and half of them receive anti-hypertensive treatment. Unfortunately, half of the subjects on treatment have poorly controlled hypertension.[3] A study from Pakistan showed that blood pressures of 12,5% of hypertensive patients were on target.[4]

The rationale of this study was to provide data on what issues need to be addressed in order to increase the control rates of hypertension.

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The aims of present study were to determine the factors associated with achieving target blood pressure levels and compare the anthropometric and clinical parameters of subjects with well-controlled hypertension to those with the poorly controlled.

METHODOLOGY

Adult hypertensive subjects treated in the clinics of Abant Izzet Baysal University Hospital, Bolu, Turkey, between January and June 2016 were enrolled. Patients with secondary hypertension, hypertension in pregnancy, and younger than 18 years of age were excluded from the study. The study was approved by local ethics committee (4th November 2015, Registration No. 174). Patients' characteristics: age, gender, systolic blood pressure, diastolic blood pressure, height, weight, duration of the disease, and waist circumference, were recorded. Laboratory data included creatinine clearance, blood urea nitrogen (BUN), plasma creatinine, sodium and potassium and serum triglyceride total , HDL and LDL cholesterol obtained and recorded from computerised database and case files of the clinic. Compliance of the subjects to treatment, number of drugs used for HT, adherence to diet and exercise programme, whether they knew definition of hypertension and normal range of blood pressure, whether and how often they measured blood pressure at home, family history for HT, duration of the disease, smoking and drinking status, living environment (rural/urban), and comorbidities were questioned.

Definition of well- and poorly-controlled hypertension based on the suggestions of JNC VIII.[5] According to these guidelines, thresholds of initiation of treatment were set as goal blood pressure levels. A single blood pressure value was obtained for each individual by taking the average of the blood pressure measurements that made at least two times from both arms at consecutive clinic visits. Thus, patients were divided into two groups: well-controlled and poorly controlled HT groups.

Body mass index (BMI) was simply calculated by dividing of body weight (in kilograms) to square of height (in meters). Subjects with a BMI value $\geq$30 kg/m^2 were defined as obese. Bound of waist circumference was based on the suggestions of Turkish Society of Endocrinology and Metabolism, which set the upper limit in men and women from Turkish ancestry at 94 cm and 84 cm, respectively.

Data were analysed by SPSS software (SPSS 15.0 for Windows, IBM, Chicago, IL, USA). Chi-square test used for analysis of categorical variables. Distribution of variables between groups were detected by Kolmogorov-Smirnov test. Homogenously distributed variables were analysed by student's t-test and data were expressed as mean ± standard deviation. Non-homogenously distributed variables were analysed by Mann-Whitney U-test and data were expressed as median (interquartile range). Statistically significance was set on a p-value of less than 0.05.

RESULTS

A total of 342 patients, 127 men and 215 women, were enrolled to the study. Of these, 193 (56.4%) were reserved into well-controlled and 149 (43,6%) were reserved into poorly controlled hypertension groups. Mean age of the well-controlled and poorly controlled hypertension groups were 63 ±11.3 and 61.5 ±10.4 years, respectively (p=0.47). Gender (p=0.15) was not statistically different between groups. Laboratory parameters were also not different between well- and poorly-controlled hypertensive subjects (p>0.05 for all). Duration of the hypertension, smoking and drinking status, family history, knowledge of the definition of hypertension, adherence to exercise and diet schedule, living environment (rural/urban), number of drugs used for control of the blood pressure, and comorbidities were not statistically different in well-controlled compared to poorly controlled hypertension groups. Table I shows general characteristics and laboratory data of the study population. Table II shows the comparison of data derived from questionnaires of study groups.

Of 342, 116 (33.9%) were aware of normal blood pressure range and 226 (66.1%) were not. Well controlled HT was significantly much more common among aware subjects than unaware patients (p=0.008).

Table I: General characteristics and laboratory values of the study groups.

	Well-controlled HT	Poorly controlled HT	p-value
Gender			
Male (n)	78	49	0.15
Female (n)	115	100	
	Mean ± standard deviation		
Age (year)	63 ±11.3	61.5 ±10.4	0.47
DBP (mmHg)	75 ±8.49	84.7 ±10.6	<0.001
BMI (kg/m^2)	30.15 ±5.1	31.54 ±6.4	0.007
Total cholesterol (mg/dl)	195.05 ±46	205.83 ±49.1	0.07
LDL cholesterol (mg/dl)	114.5 ±38.9	126.63 ±42.5	0.14
HDL cholesterol (mg/dl)	45.32 ±10.28	45 ±9.4	0.7
	Median (IQR)		
SBP (mmHg)	130 (12)	153 (16)	<0.001
Urea (mg/dl)	32 (15)	32 (13)	0.97
Creatinine (mg/dl)	0.81 (0.31)	0.81 (0.29)	0.74
Na (mmol/dl)	139 (4)	139 (4)	0.71
K (mmol/dl)	4.45 (0.6)	4.5 (0.5)	0.2
Triglyceride (mg/dl)	132.5 (104)	142 (77)	0.24
Duration of HT (year)	10 (10)	10 (10)	0.8
Waist circumference (cm)	99.5 (19,3)	104 (18,8)	<0.001
GFR (ml/dk/1.73m^2)	85.5 (32)	86.5 (25)	0.87

DBP= Diastolic blood pressure; SBP = Systolic blood pressure; BMI = Body mass index; Na = Plasma sodium; K = Plasma potassium; t-test, Mann-Whitney U-test.

Table II: Data from questionnaires of the study groups.

	Well-controlled HT	Poorly controlled HT	p-value
Therapeutic compliance (n, %)			
Complied with treatment	130 (62.8%)	77 (37.2%)	0.003
Non-complied with treatment	63 (46.6%)	72 (53.4%)	
Family history of HT (n, %)			
Positive	162 (57.2%)	121 (42.8%)	0.50
Negative	31 (52.5%)	28 (47.5%)	
Exercise schedule (n, %)			
Adherent	70 (56.5%)	54 (43.5%)	0.99
Non-adherent	123 (56.4%)	95 (43.6%)	
Diet (n, %)			
Adherent	82 (60.7%)	53 (39.3%)	0.20
Non-adherent	111 (53.6%)	96 (46.4%)	
Awareness of normal BP ranges (n, %)			
Aware	77 (66.4%)	39 (33.6%)	0.008
Unaware	116 (51.7%)	110 (48.7%)	
Living environment (n, %)			
Rural	149 (55.8%)	118 (44.2%)	0.66
Urban	44 (58.7%)	31 (41.3%)	
Cigarette smoking (n, %)			
Smokers	48 (59.3%)	33 (40.7%)	0.56
Non-smokers	145 (55.6%)	116 (44.4%)	
Alcohol drinking (n, %)			
Drinkers	48 (59.3%)	33 (40.7%)	0.30
Non-drinkers	145 (55.6%)	116 (44.4%)	
Comorbidities (n, %)			
Present	132 (57.5%)	98 (42.6%)	0.60
Absent	61 (54.5%)	51 (45.5%)	
Antihypertensive medicine (n, %)			
One drug	63 (58.9%)	44 (41.1%)	0.54
Two or more drugs	130 (55.3%)	105 (44.7%)	
Self-measurement of BP at home (n, %)			
Yes	162 (57.4%)	120 (42.6%)	0.41
No	31 (51.7%)	29 (48.3%)	
Duration of HT (n, %)			
$\geq$10 years	82 (41.3%)	60 (40.2%)	0.62
<10 years	111 (58.7%)	89 (59.8%)	

BP = Blood pressure; HT = Hypertension; Chi-square test.

Treatment compliance was significantly associated with better control of hypertension. Of 342, 207 (60.5%) were complied with antihypertensive treatment and 135 (39.5%) were not. While 62.8% of complied subjects' blood pressures were on target, only 46.6% of patients without compliance had well controlled HT. The difference between groups were statistically significant (p=0.003).

Waist circumference and BMI of the well-controlled HT subjects were 99.5 (19,3) cm and 30.2 ±5.1 kg/m^2, respectively. These measures were higher in poorly controlled HT subjects (waist circumference: 104 (18,8) cm, BMI: 31.5 ±6.4 kg/m^2). The difference between well and poorly controlled HT groups was statistically significant (p=0.001 for waist circumference and p=0.007 for BMI).

DISCUSSION

Present study showed that control of the blood pressure is mostly affected by BMI, waist circumference, adherence to treatment, and awareness of the normal blood pressure range.

Most of the study population in this report were women. About 81% of the study population were women and 19% were men in a prevalence study of hypertension in literature.[3,6] Besides, incidence of HT is more common in females; greater awareness of the disease among this gender may contribute to gender predisposition.[7] Framingham study showed that HT rates were increased by elevation of BMI in population.[8] On the other hand, it is reported in NHANES II that HT prevalence was six times higher in 20-45 years of age subjects with a BMI greater than 27kg/m^2 compared to those with a lower BMI.[9] Similar but from another view point of the literature, we found that increased BMI was associated with poorly controlled blood pressure.

Waist circumference of poorly controlled HT group was significantly larger than that of the well-controlled subjects in this study. Increased waist circumference, as a result of abdominal obesity, has been shown to be associated with higher blood pressure levels.[10] An interesting report showed that 93% of HT patients had elevated waist circumference.[11] As a component of metabolic syndrome, increased waist circumference causes not only insulin resistance but also high blood pressure.

Treatment compliance was significantly higher in well controlled HT compared to poorly controlled hypertensive patients. Lack of compliance is an important cause of treatment failure or treatment resistance. Only about 74% of hypertensive patients were compliant to treatment in a study by Col *et al*.[6] A study from Italy reported 41% of discontinuation of treatment for hypertensive patients, which means 59% of compliance.[12] Compliance was 60.5% in this report which was comparable to the results in literature. Poorly controlled blood pressure is an expected result of incompliance. Cessation of antihypertensive drugs after normalisation of blood pressure, forgetfulness to take medicine and insufficient dosage are possible causes of therapeutic incompliance.

Blood pressure has tight junctions with diet and lifestyle. Obesity and related disorders, such as HT, increased in developing countries as a result of reduced physical activity and high calorie intake.[13,14] Diet and physical activity are the most important and cost-effective treatment options of obesity and also necessary in prevention and control of hypertension.[15] Brisk walking for 30 minutes at least five days a week reduces systolic and diastolic blood pressures by 9 and 8 mmHg, respectively.[16] However, control rates of blood pressure were not different in patients that adherent to diet and exercise schedules and who were not in present study. Possible factors that caused this result may be cessation of adherence to diet and exercise after normalisation of blood pressure following treatment initiation, lack of adequate patient education that emphasize the importance of these approaches in antihypertensive therapy.

Control rate of blood pressure was significantly higher in patients who were aware of normal blood pressure ranges than that of who were not. One hundred and sixteen (34%) patients of study population were aware of normal ranges of blood pressure and this finding was compatible with the data in literature. Studies reported ratio of blood pressure awareness about 30%.[17]

Physicians should pay special attention in educating or informing patients about the disease, particularly definition of HT, normal blood pressure ranges, and self-measuring of blood pressure at home. Hypertensive patients, who understood that their blood pressure is above normal limits, may be more eager to implement initiatives to control blood pressure such as therapeutic compliance and lifestyle modifications. It has been reported in a study that patient education about HT was more important than antihypertensive regimens in achieving well-control of blood pressure.[18] Besides HT, patient-education has also been associated with better control of the disease in diabetic individuals.[19]

Education of hypertensive patients makes them more active and responsible in therapeutic process, ready to perform self-measurement of blood pressure, and more determined to apply lifestyle modifications.[20,21] Indeed, as a part of patient education, kiosks in HT clinics, which give brief information to the subjects about disease, have significantly contributed to achieve target blood pressure levels.[22]

CONCLUSION

Therapeutic compliance, awareness of normal blood pressure ranges and reducing BMI and weight circum-

ference are essential interventions for reaching blood pressure targets in HT patients. Awareness of normal blood pressure ranges, therapeutic compliance, reducing BMI and waist circumference, were the results of physicians' devoted endeavour in patient.

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ORIGINAL ARTICLE

Outcome of Total Laparoscopic Hysterectomy

Samina Saleem Dojki and Alia Bano

ABSTRACT

Objective: To determine the surgical outcomes of total laparoscopic hysterectomy performed.
Study Design: Case series.
Place and Duration of Study: Obstetrics and Gynecologic Endoscopic Unit of Patel Hospital, Karachi, from February 2013 till February 2016.
Methodology: The study included all patients on whom total laparoscopic hysterectomy was performed during the study period. Patients with malignancy were excluded from the study, except those with suspected stage 1 and 2 endometrial carcinoma. The procedures were performed by two gynecologists keeping rest of the team constant, with similar technique. The reviewed outcome measures were duration of surgery, and intraoperative and postoperative complications.
Results: Out of 209 patients, majority were multiparous with median age and weight of 45 (50-40) years and 69 (80-60) Kgs, respectively. Previous history of abdominopelvic surgery was present in 33%. Heavy menstrual bleeding was the leading indication. Median and interquartile value of operative time was 175 (225-120) minutes. Total rate of intraoperative and postoperative complications was 12.9% and major complications were 3.8%. All postoperative complications were minor. Of all, 3.3% of patients were converted to open surgery; there was no vascular injury or re-operation.
Conclusion: Total laparoscopic hysterectomy is safe, acceptable, and doable alternative to conventional standard hysterectomy.

Key Words: *Laparoscopy. Hysterectomy. Complications. Laparoscopic hysterectomy.*

INTRODUCTION

Hysterectomy is one of the commonest surgical procedures performed in gynecology worldwide.[1] The common indications are fibroid uterus, endometrial pathology, endometriosis, and ovarian tumors. Laparoscopic method for gynecological indications has gained popularity over the last 20 years, in terms of safety as well as patient convenience. Gynecologic endoscopy is no longer restricted to diagnostic or simpler procedures. The approach is frequently being used now for varied indications. Even acute pelvic emergencies,[2] are being performed by minimal access. After the first laparoscopic hysterectomy in 1989 by Harvey Reich,[3] there had been many advances in technique and instrumentation. These innovations and gynecologists' persistence have led to rapid progress in minimal invasive surgeries like robotics and natural orifice transluminal endoscopies. He *et al*., have shown that these advances have resulted in better and comparable results for laparoscopic approach and resulted in lesser intraoperative blood loss, shorter hospital stay and quicker recovery.[4]

In experienced hands with well selected patient, the results of total laparoscopic hysterectomy (TLH) are comparable to those of vaginal hysterectomy in terms of postoperative parameters and patient satisfaction.[5] Time taken for the procedure is more to begin with as it has its learning curve but as one gains experience, its duration reduces markedly. The other approaches for hysterectomy are open abdominal hysterectomy and vaginal hysterectomy. For years, vaginal hysterectomy is preferred over other routes, especially for uterovaginal prolapse.[6,7] Literature is not available for TLH from Pakistan due to lack of training opportunities as well as acceptance of change among gynecologists.[8,9] This can be overcome by proving its advantages through local data.

The aim of this study was to determine the surgical outcomes of total laparoscopic hysterectomy.

METHODOLOGY

The records of all patients who underwent TLH during February 2013 to February 2016 were included in the study. The data was reviewed and collected prospectively from patients' files by the postgraduate trainees and entered on a predesigned proforma. The study proposal was submitted to Hospital Ethics Committee and was granted exemption as patients' identity was not revealed. The surgery was performed by one of the two authors with an additional diploma in gynaecologic endoscopy. The study population included patients of all ages, parity, and weight. The patients with benign disease, probable stage 1 and 2 endometrial malignancy as well as borderline ovarian malignancy were also included in the study. The demographics, indications, duration of surgery, presence or absence of previous abdominal/pelvic surgeries, intraoperative and

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postoperative outcomes, and duration of indwelling catheter and hospital stay were reviewed.

The outcomes were categorised into major and minor complications. Major complications were defined as hemorrhage requiring transfusion, vascular injury, injury to the bowel, bladder or ureter, laproconversion or re-operation and complete vault dehiscence. Minor complications were defined as any infection or temperature of more than 38º C on two occasions six hours apart (excluding the first 24 hours after surgery), port site infection (PSI), vault infection, and partial vaginal vault dehiscence. Blood loss was measured by the volume of blood contained in suction bottle before irrigation is used or if irrigation was already used, the saline volume was deducted. Surgical duration was calculated in minutes from skin incision till skin closure. The patients were followed up at two weeks and then at six weeks.

Analysis was conducted with statistical package for social science (SPSS) version 21. Shapiro-Wilk test was applied to check the normality of the data. Statistical analysis included simple descriptive analysis of the study variables in terms of median (IQR); whereas, frequencies and percentages of qualitative data were computed. Due care was taken to keep the patient confidentiality, and the identity was marked.

RESULTS

During the study period, 209 patients underwent total laparoscopic hysterectomy. Patients' demographic and clinical characteristics including age, parity, weight, previous abdominopelvic surgeries including Caesarean deliveries, uterine weight, and indications for the procedure are displayed in Table I. The median age and weight of the women were 45 (50-40) years and 69 (80-60) kgs, respectively. Majority, 133 (63.6%) of patients were multiparous. Uterine volume ranged from normal to 18-week size. The largest uterus weighed 782 grams. Previous history of abdomino-pelvic surgery was present in 69 (33%), in which 32 (15.76%) had one or more Caesarean sections and 27 (13%) had more than one type of surgery. Heavy menstrual bleeding (HMB) was the commonest indication, followed by uterine fibroid uterus.

Estimated blood loss, more than 100 ml, was found in 6 (2.9%), median and interquartile value of operative time was 175 (225-120) minutes, hours of postoperative indwelling catheterisation were 7 (8-5) hours and duration of postoperative hospital stay was 1 (2-1) day.

The intra- and post-operative complications are detailed in Table II. Total number of intra- and post-operative complications was 29 (13.9%). Major complications were observed in 8 (3.87%) patients. These major complications included two sigmoidal tears and one ureteric injury. Of the two sigmoid injuries, one was managed by laparoscopic suturing. The other sigmoid injury and one ureteric injury ended up in laproconversion and repair. Dense bowel adhesions were observed in four cases after primary port entry and they were converted to laparotomy. There was one more conversion due to failure of entry into the abdomen that made it total 7 (3.3%) conversions.

Postoperative complications were observed in 15 (7.1%) cases. All were minor including five port site infections;

Table I: Baseline characteristics of patients and indications for surgery.

Median age of the patients	45 (50-40)
Parity distribution	
Multiparous	133 (63.6%)
Grand multiparous	50 (23.9%)
Parity 1	14 (6.7%)
Nulliparous	12 (5.75)
Median (IQR) weight of uterus	140 (76)
Previous abdomino pelvic surgery	
No	140 (67%)
Yes	69 (33%)
Previous LSCS	
No Previous LSCS	175 (83.7%)
Previous 1 LSCS	19 (9.1%)
Previous 2 LSCS	7 (3.3%)
Previous 3 LSCS	7 (3.3%)
Previous 4 LSCS	1 (0.5%)
Indication of surgery	
Heavy menstrual bleeding	65 (31.1%)
Fibroid	62 (29.7%)
Thickened endometrium	20 (9.6%)
Ovarian cyst	18 (8.6%)
Post-menopausal bleeding	17 (8.1%)
Endometrial polyp	8 (3.8%)
Endometriosis	4 (1.9%)
Pelvic inflammatory disease	4 (1.9%)
Fibroid + ovarian cyst	3 (1.4%)
Cervical polyp	2 (1%)
Carcinoma ovary	2 (1%)
Ca Endometrium	1 (0.5%)
Chronic pelvic pain	1 (0.5%)
Endometrial polyp	1 (0.5%)
Dyspareunia	1 (0.5%)

Table II: Intraoperative and postoperative complications.

Per- and post-operative complications	
No	180 (86.1%)
Yes	29 (13.9%)
Per-operative complications	
No complications	195 (93.3%)
Estimated blood loss >100	6 (2.9%)
Conversion	6 (2.9%)
Bowel injury	1 (0.5%)
Conversion + bowl + bladder injury	10.5%)
Post-op complications	
No complication	193 (92.3%)
Fever	6 (2.9%)
Wound infection	5 (2.4%)
Partial vault dehiscence	2 (1%)
Vault infection	3 (1.4%)

fever was reported in six. One patient had partial vault dehiscence, while three cases of vault infections were observed. All responded to conservative management. There was no vascular injury and no patient received intraoperative or postoperative blood transfusion and ICU transfer. None case required re-operation.

Postoperatively, all patients were mobilised 4-6 hours after surgery and Foley's catheter was removed at the same time. Most of the patients were discharged within 24 hours after surgery.

DISCUSSION

The study documents a series of 209 consecutive total laparoscopic hysterectomies. The demographics of this study are similar to the study done by Vincent with respect to age (mean 45 years vs. 47 years) and weight (mean 69 Kgs vs. 67 Kgs).[10] History of one or more C sections was more 32% in this series vs. 12.6%.[10] Both studies included wide range of age and parity. Similarly, weight was not the exclusion criteria and the study encompassed the weight from lean to morbidly obese. This helps in drawing results from wide variety of sample. Literature also supports that neither age, weight nor parity or previous abdominal surgeries is a limitation.[10-12] Conventionally, history of previous abdominopelvic surgery has been considered as a risk factor for complications and a factor of prolonged surgical time. This study did not exclude this factor; Cem Celik and Remzi Abal have already reported equivalent results for patients with or without such history.[13]

Median and interquartile value of operative time was 175 (225-120) minutes, which is comparable to those studies done in initial years by Nezhat *et al*., which was 160 minutes;[14] while it is little more when compared to 111.5 minutes in his more recent study.[15] This depicts the effect of learning curve when surgeons show consistency.

The major complication rate reported in literature by Hoffman *et al*. and Heinberg *et al*. range from 5.6% and 14.4%, respectively,[16,17] while Chaperon reported complications in 10% cases in his study.[18] The major complications rate in our study was 3.87%. The lesser number of complications in this study is encouraging.[19] This may also imply the need of a larger number of surgeries and then comparing with bigger local and international studies.

There was one ureteric injury (0.478%) in a patient with endometriosis, which was recognised and repaired by the urologist at the same time. The reported incidence of ureteric injuries in literature is 0.2% to 2%,[19] and corresponds well to that in the current study.

In 2012, Jensen *et al*. reported access-related bowel injuries to be 4.4/10,000 procedures,[20] while it was not seen in this study. There were only two superficial sigmoid injuries (0.95%), one was thermal and another one was a tear during adhesinolysis due to endometriosis; and both were recognised and repaired intraoperatively.

The conversion rate of 3.3% is much less than that quoted by a French study, which reported 7% conversions in a group of 416 patients.[21]

The minor complications, though in a bigger number than major ones, all were managed conservatively; none required surgical intervention. The most troublesome of these partial vault dehiscence was only 1 (0.47%). This is comparable to 0.39% reported by Hur *et al*. in his recent study in 2011,[21] and much less than his earlier reported incidence of 4.9% in 2007.[22] In his study, majority experienced complete vault dehiscence and needed surgical repair, while our patient was managed conservatively. The rest of the minor complications were low grade fever for one or two days, vaginal discharge due to vault infection. Both of these responded well to antibiotics. Port site infection after all sorts of laparoscopic surgeries is rare but can be so much bothersome that it might undermine the benefits of this minimal invasive approach. The overall incidence of umbilical PSI has been reported as 8% with maximum being after laparoscopic cholecystectomy.[23]

The debate about the route of this commonly needed procedure is, for years now, relates to the surgical time and the rate of complications. Now, as more and more the procedures are being performed and more advanced techniques and instruments are being innovated, the results are comparable on both aspects. The better results regarding early recovery and better cosmetic value are already known.

The strength of this study was similar technique of all cases done by only two surgeons. Also the sample size is good, considering the first study from a country. This is the first ever study on laparoscopic hysterectomy from our country, so the results cannot be compared with local literature. The limitation in the study was that the general surgeons and urologists in our institute perform open surgeries only which led to option of laparoscopic conversion in visceral injuries.

CONCLUSION

The demographics, varied indications, previous history of surgeries, and the outcomes show that a wide range of patients can be provided with the emerging facility of laparoscopic hysterectomy. The current study outcome measures correlate well with recent international literature. Laparoscopic hysterectomy is safe and a doable method. Appropriate training in minimal invasive surgery and skills are fundamental. This recommendation needs vigour by more local data; a dire need of time.

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ORIGINAL ARTICLE

Vital Sign Variations with Complications during Dialysis among End-Stage Renal Disease Patients

Abdul Rehman Qureshi[1], Naureen Durrani[2] and Naila Asif[3]

Abstract

Objective: To analyse the association of vital sign variations with complications during dialysis among end-stage renal disease patients.

Study Design: Cross-sectional study.

Place and Duration of Study: Dialysis Centre, Memon Medical Institute Hospital, Karachi, Pakistan, from December 2016 to February 2017.

Methodology: Patients on regular hemodialysis with permanent vascular access were selected. Analysis was done during their regular hemodialysis session. Vital signs were measured before and after dialysis, and ultrafiltration (in litre) was recorded post-dialysis. Complications and the variations in vital sign during dialysis were documented as 'yes' or 'no' on the proforma. The association of vital sign on complications during dialysis was analysed by using Pearson Chi-square or Fisher Exact test. A p-value <0.05 was considered statistically significant.

Results: Among the study participants, 250 (65.78%) were males and 130 (34.21) were females. Overall mean age and ultrafiltration rate were 51.89 ±15.83 years and 2.11 ±0.99, respectively. Most of the patients suffered with complications of cramps during dialysis, i.e. 151 (39.73%) followed by complication of hypotension 143 (37.63%). Significant association was observed only in variation in systolic blood pressure with complication of hypotension (p<0.001), followed by variation in body weight with complication of cramps (p=0.016) and hypotension (p=0.037).

Conclusion: Vital signs variations, i.e. variation in systolic blood pressure and variation in body weight, are associated with intradialytic complications, i.e. hypotension and hypotension with cramps, respectively.

Key Words: *Hemodialysis. Hypotension. Intradialytic complications.*

INTRODUCTION

Renal failure can be acute or chronic, depending upon duration of injury.[1] Both can be managed conservatively or with renal replacement therapy (RRT), depending upon the clinical scenario.[2] RRT includes hemodialysis (HD), continuous renal replacement therapy (CRRT), peritoneal dialysis (PD) and renal transplantation. Once a patient has reached stage IV chronic kidney disease (CKD), with size adjusted estimated glomerular filtration rate (eGFR/1.73m^2) of <30ml/min, they should be under a nephrologist's care, who would then determine future treatment options.[2] The decision to start hemodialysis in CKD stage 5 depends on one or more of the following being present: symptoms or signs attributable to kidney failure (serositis, acid-base or electrolyte abnormalities, pruritus); inability to control volume status or blood pressure; a progressive deterioration in nutritional status refractory to dietary intervention; or cognitive impairment.[2]

There have been certain hemodynamic changes and specific vital signs variations during each dialysis session, which may affect the quality of life in the long run.[3,4] Recent data from India shows how specific variations in vital signs, and regular dialysis maintained the specifications of vital signs parameters among dialysis patients.[5] Maintenance of dialysis patients usually experiences multiple complications during dialysis, which include hypotension (may manifest as dizziness), cramps, nausea, vomiting, headaches, chest pain, and/or shortness of breath.[6]

It is assumed that there can be direct or indirect link of vital signs variations with certain intradialytic complications. However, at present there is no such documented literature to explain these discrepancies, as per authors' knowledge.

The objective of this study was to observe the association of vital signs variations on clinical symptoms or complications during dialysis.

METHODOLOGY

A cross-sectional study was conducted at the Dialysis Centre, Memon Medical Institute Hospital, Karachi, Pakistan from December 2016 to February 2017. Single-population proportion formula was applied to find the

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sample for the study. The highest prevalence for hypotension, reported in previous studies,[12] which is 0.55. 5% level of significance and 95% confidence interval, has been used for the calculation of sample size. Patients of either gender who were undergoing regular maintenance of hemodialysis with permanent vascular access in place were selected. Analysis was done during their regular hemodialysis sessions. Data were collected upon approval from the Ethics Review Committee of the institution. Patients with a hemoglobin level of less than 10 gm/dl, ischemic heart disease or with active inflammatory disease were excluded. Single-use dialyser session was observed. Vital signs such as weight measurement, blood pressure, and heart rate were measured before and after dialysis, and ultra-filtration was recorded post-dialysis. There was a standard protocol for holding anti-hypertensive medications on the day of dialysis to reduce the effects of medications. However, data of beta blockers and non-dihydropyridine was collected. An adjustment for the intake of beta blockers and non-dihydropyridine calcium channel blockers was done while analysing the data.

Intradialytic blood pessure variation was defined as change of 10 mmHg (systolic blood pressure) during dialysis.[7] Intradialytic hypotension (IDH) was defined as systolic BP less than 90 mmHg or fall in systolic BP of 20 mmHg.[8] Equivalent to or more than 10 beats per minute range in heart rate was considered as heart rate variation recorded before and at the end of dialysis as single episode.[9] Equivalent to or more than 0.5 kilogram (equivalent to 500 ml ultrafiltrate) was used as body weight variation over four hour of dialysis. Complications (chest pain, hypotension, cramps, nausea/vomiting and faintness) during dialysis were documented as 'yes' or 'no' on proforma. The variations in vital signs were coded as 'yes' or 'no' as well.

Demographic variables were summarised by using descriptive statistics in terms of mean with standard deviation or percentages and frequencies, where necessary. The association of vital signs on complications during dialysis was analysed by using Pearson Chi-square or Fisher Exact test. All analyses were performed using SPSS version 21. A p-value <0.05 was considered statistically significant.

RESULTS

Patients' demographics are given in Table I. Among the study participants, 250 (65.78%) were males and 130 (34.21) were females. Overall mean age and ultra-filtration (litre) were 51.89 ±15.83 years and 2.11 ±0.99, respectively. One hundred and eighty-one (47.63%) patients were on beta blocker, out of which, 151 (83.42%) patients were on Metaprolol, 22 (12.15%) were on Carvedilol, and 8 (4.41%) patients were on Bisoprolol. None of the patient is on non-dihydropyridine. Average duration of hemodialysis sessions was around four hours. Blood flow rate was 350 ml/min. The included sample comprises of 221 (58.16%) diabetic patients of both the gender, out of 380 participants. Most of the patients suffered with complications of cramps during dialysis, i.e. 151 (39.73%) patients experienced cramps in legs during dialysis. One hundred and forty-three (37.63%) were observed to be hypotensive during dialysis. Chest pain occurred in 44 (11.57%) patients during the session of dialysis. Tweny-two (5.78%) patients developed nausea/vomiting and headaches when on dialysis. Faintness was seen in only 7 (1.84%) during the sessions.

Table I: Patients' demographics.

Demographic variables	Mean ± SD or Total (percentage)
Age	51.89 ±15.83
Ultrafiltration (liter)	2.11 ±0.99
Diabetic	
Yes	221 (58.16%)
No	159 (41.84%)
Beta blocker	
Yes	181 (47.63%)
Metaprolol	151 (83.42%)
Carvedilol	22 (12.15%)
Bisoprolol	8 (4.41%)
No	199 (52.36%)
Non-dihydropyridine calcium channel blocker	
Verapemil	0 (0%)
Diltiazem	0 (0%)
No	380 (100%)
Gender	
Male	250 (65.78%)
Female	130 (34.21%)
Complications	
Chest pain	44 (11.57%)
Cramps	151 (39.73%)
Hypotension	143 (37.63%)
Faintness	7 (1.84%)
Nausea/vomiting	22 (5.78%)
Others (headache)	22 (5.78%)

Significant association was observed only in two groups: variation in systolic blood pressure with complication of hypotension ($p<0.001$), followed by variation in body weight with complication of cramps ($p=0.016$), and hypotension ($p=0.037$, Table II). There was no significant association of heart rate variation with any complication (Table II). None of the remaining complications were found to be significantly associated with the other three groups i.e. variation in blood pressure, variation in heart rate, or variation in body weight (ultrafiltrate in litre).

Diabetic patients group was significantly associated with variation in heart rate ($p=0.009$, Table II). There were 79 (20.78%) diabetic in whom heart rate variations were observed and 142 (37.36%) diabetic patients did not experience heart rate variation. Seventy-eight (20.52%) were those non-diabetic patients who suffered with variation of heart rate. There is not a huge difference between those diabetic patients who were suffered with

heart variation; however, this difference is significant. There will be no significant association of non-dihydropyridine with any of the comparison group as none of the patients is found to be with non-dihydropyridine. The number of patients who were on beta blocker are significantly higher in group of those who were suffered with variation in blood pressure (p=0.016, Table II). Most of the patients were on metoprolol (30.52%) who suffered with variation in blood pressure. Thus, beta blocker is significantly associated with variation in blood pressure.

The occurrence of those complications that were significantly associated with ultrafiltration rate was more in patients as compared to those complications that

Table II: Significant association of complications in three variations.

Complications	Variation in blood pressure (systolic)			Variation in heart rate			Variation in body weight		
	P-value	No Number (%)	Yes Number (%)	P-value	No Number (%)	Yes Number (%)	P-value	No Number (%)	Yes Number (%)
Chest pain									
Yes	0.618	12 (3.16)	32 (8.42)	0.092	31 (8.16)	13 (3.42)	0.378	0 (0.00)	44 (11.57)
No		104 (27.37)	232 (61.05)		192 (50.53)	144 (37.89)		13 (3.42)	323 (85.00)
Cramps									
Yes	0.106	39 (10.26)	112 (29.47)	0.105	81 (21.31)	70 (18.42)	0.016*	1 (0.26)	150 (39.47)
No		77 (20.26)	152 (40.00)		142 (37.36)	87 (22.89)		12 (3.15)	217 (57.10)
Hypotension									
Yes	*<0.001	5 (1.32)	138 (36.32)	0.680	82 (21.57)	61 (16.05)	0.037*	1 (0.26)	142 (37.36)
No		111(29.21)	126 (33.16)		141 (37.10)	96 (25.26)		12 (3.15)	225 (59.21)
Faintness									
Yes	0.680	1 (0.26)	6 (1.58)	0.705	5 (1.31)	2 (0.52)	1.000	0 (0.00)	7 (1.84)
No		115 (30.26)	258 (67.89)		218 (57.36)	155 (40.78)		13 (3.42)	360 (94.73)
Nausea/vomiting									
Yes	0.276	9 (2.37)	13 (3.42)	0.627	14 (3.68)	8 (2.10)	1.000	0 (0.00)	22 (5.78)
No		107 (28.16)	251 (66.05)		209 (55.00)	149 (39.21)		13 (3.42)	345 (90.78)
Headache									
Yes	0.540	8 (2.10)	14 (3.68)	0.968	13 (3.42)	9 (2.36)	0.545	1 (0.26)	21 (5.52)
No		108 (28.42)	250 (65.78)		210 (55.26)	148 (38.94)		12 (3.15)	346 (91.05)
Diabetic									
Yes	0.056	59 (15.52)	162 (42.63)	0.009	142 (37.36)	79 (20.78)	0.143	5 (1.31)	216 (56.84)
No		57 (0.15)	102 (26.84)		81 (21.31)	78 (20.52)		8 (2.10)	151 (39.73)
Beta blocker									
Metoprolol	0.016	35 (9.21)	116 (30.52)	0.300	88 (23.15)	63 (16.57)	0.533	3 (0.78)	148 (38.94)
Carvedilol		4 (1.05)	18 (4.73)		15 (3.94)	7 (1.84)		1 (0.26)	21 (5.52)
Bisoprolol		2 (0.52)	6 (1.57)		7 (18.42)	1 (0.26)		0 (0.00)	8 (21.05)
No		75 (19.73)	124 (32.63)		113 (29.73)	86 (22.63)		9 (2.36)	190 (50)

Table III: Significant association of complications in ultrafiltration categories.

Complications	Ultrafiltration categories				
	1 (0-1 Litre)	2 (1.1-2 Litre)	3 (2.1-3 Litre)	4 (>3Litre)	p-value
Chest pain					
Yes	7	9	20	8	0.220
No	57	116	109	54	
Cramps					
Yes	15	52	56	28	0.033*
No	49	73	73	34	
Hypotension					
Yes	18	40	58	27	0.045*
No	46	85	71	35	
Faintness					
Yes	1	1	4	1	0.588
No	63	124	125	61	
Nausea/vomiting					
Yes	4	8	6	4	0.923
No	60	117	123	58	
Headache					
Yes	7	4	8	3	0.224
No	57	119	120	59	

were not significantly associated with ultrafiltration rate. Cramps (p=0.033) and hypotension (p=0.045) were found to be associated with increases in ultrafiltration rate (Table III).

DISCUSSION

Kidneys are important and vital organs of body, which perform multiple functions which include removal of waste products (urea and creatinine), production of erythropoiten, regulation of vitamin D, metabolism, and regulation of the renin-angiotensin system. If any abnormality occurs in these functions then patient is labelled as case of chronic kidney disease.[2] Once CKD stage 5 is reached then nephrologist decides about treatment options depending upon clinical symptoms,[2] including renal replacement therapy in the form of hemodialysis, peritoneal dialysis or renal transplantation.[10]

Hemodialysis is a process whereby the solute composition of solution A is altered by exposing it to a second solution B through a semipermeable membrane.[11] In hemodialysis (HD), solute clearance from the blood is achieved by diffusion across the membrane, driven by a concentration gradient between the blood and dialysate.[11]

Intradialytic hypotension (IDH) is defined as systolic BP less than 90 mmHg or fall in systolic BP of 20 or 30 mmHg.[8] IDH occurs in 25-55% of dialysis treatments.[12] IDH is important not only because it can cause distressing symptoms, but because it is associated with poor long-term outcomes. Patients with IDH show increased mortality.[8] Muscle cramps occur in 5-20% of patients, late during dialysis and frequently involving the lower limbs. They account for 15% of premature discontinuation of dialysis.[13] Nausea or vomiting occurs in up to 5-15% of routine dialysis treatments, the causes can be multifactorial.[12] Headaches occurs in as many as 5% of patients, and may become intense and throbbing.[12] Mild chest pain or discomfort (often associated with some back pain) occurs in 1-4% of dialysis treatments.

Intradialytic hypotension is the most common complication observed during dialysis.[12] In this study, it was the second most complication (37.63%) after muscle cramps. It is associated with increased mortality, and increased rate of myocardial stunning.[8-14] Patients at increased risk of intradialytic hypotension include those who have diabetes, cardiovascular diseases, poor nutritional status, severe anemia, requiring high volume ultrafiltration, and those with a predialysis systolic blood pressure of <100 mmHg. Volume related complications are most important as significantly proven in our study (p=0.045) as mentioned in Table III and can be controlled by maneuvers to slow ultrafiltrate (by extending the weekly time on dialysis, reducing the weekly volume of fluid ingestion and increasing the volume of urine excreted). Other measures to reduce intradialytic hypotension are temperature, and sodium profiling,[15-17] avoiding intradialytic food ingestion, avoiding antihypertensive medication, slowing blood flow rate during dialysis and maintaining hemoglobin (10-11 g/dl).

Muscle cramps are the major complication (39.73%) observed in this study as compared to literature (5-20%).[9] Hypotension, hypovolemia, high ultrafiltration rate (large weight gain), and use of low-sodium dialysis solution are the four most important predisposing factors resulting in muscle hypoperfusion leading to secondary impairment of muscle relaxation and causing muscle cramps.[18] In this study, it is observed in change in body weight (p=0.016) and increasingly associated with large fluid removal (p=0.033).

Causes of nausea and vomiting are multifactorial including hypotension, dialysis disequilibrium syndrome, and gastropresis.[19] No significant association related to change in systolic blood pressure, heart rate variation, or ultrafiltrate volume (change in body weight) was found in our study. Dialysis headache is common and is explained by bifrontal discomfort.[20,21] However, chest pain, faintness and headache were observed in dialysis patients in small percentages and are not associated with any significant p-value.

All diabetic and non-diabetic patients were included in this study. Therefore, diabetic autonomic neuropathy, can be the biased factor for hypotension.[22] Dialysis machines' conductivity, was checked by biomedical team at the start of study and was not checked regularly during each session.[23] Some patients were dialysed after 48 hours and some after 72 hours, depending upon their schedule; so ultrafiltrate (in litre) could be higher in those who were dialysed after 72 hours.

CONCLUSION

Vital signs variations, i.e. variation in systolic blood pressure and variation in body weight are associated with intradialytic complications, i.e. hypotension and hypotension with cramps, respectively. However, diabetic nephropathy, interval during dialysis sessions with higher ultrafiltrate (in litre) and beta-blocker can also be associated with these complications.

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ORIGINAL ARTICLE

Histopathological Spectrum and Short-Term Outcome of Treatment with Cyclophosphamide in Relapsing Steroid-Sensitive Nephrotic Syndrome

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ABSTRACT

Objective: To determine the short-term outcome of cyclophosphamide (CPO) course in children with relapsing steroid sensitive nephrotic syndrome (SSNS) with different histopathological lesions.

Study Design: Descriptive, observational study.

Place and Duration of Study: Pediatric Nephrology Department, Sindh Institute of Urology and Transplantation, Karachi, from January 2012 to December 2014.

Methodology: All children with relapsing steroid-sensitive nephrotic syndrome, who underwent renal biopsy and received cyclophosphamide therapy, were included and followed up for 2 years. Histopathological features in renal biopsy, duration of treatment, duration of complete remission and complication frequency was noted.

Results: Of the total 74 patients, 47 (63.5%) were males and 27 (36.5%) females. Median age with Interquartile range (IQR) at presentation was 5 years (4-7 years). Minimal change disease (MCD) was the most common histopathological diagnosis (n=54, 73%) followed by focal segmental glomerulosclerosis (FSGS) (n=13, 17.5%), mesangioproliferative glomerulonephritis (MesPGN) (n=6, 8.1%), IgA nephropathy (n=1, 1.4%). The median number of glomeruli included in each biopsy sample was 15. The median duration of treatment with CPO was 11 weeks (9 to 13 weeks), whereas the median duration of complete remission post-therapy was 13 months (7-23 months). A median timeframe of 17 months (13-24.2 months) lapsed between establishing the diagnosis of NS and initiating CPO treatment. Leucopenia was noted in six (8.1%) patients.

Conclusion: The short-term outcome of relapsing SSNS can be improved with CPO and steroids, with minimum short-term side effects.

Key Words: *Relapsing steroid-sensitive nephrotic syndrome. Cyclophosphamide. MCD. FSGS. Mesangioproliferative glomerulonephritis (MesPGN).*

INTRODUCTION

Nephrotic syndrome (NS) is a common childhood renal disease characterised by a remitting and relapsing course.[1] The reported incidence is 2-7 per 100,000 children and the prevalence is 16 per 100,000 children.[2] More than 90% children with Idiopathic NS (INS) are responsive to initial treatment with steroids. However, 70-80 % of these children relapse after the first episode and 50% thereafter developing relapsing nephrotic syndrome.[3]

Relapsing episodes of steroid sensitive nephrotic syndrome (SSNS) are treated with steroid sparing agents including Cyclophosphamide (CPO), Cyclosporine, MMF and Tacrolimus. Role of CPO in the management of SDNS is well established with a total treatment duration of 12 weeks and cumulative dose of 168 mg/Kg.[4] Adverse effects with CPO are seen when the cumulative dose exceeds 200 mg/kg.[4] At the study centre, the treatment protocol employs a daily dose of 2 - 2.5 mg/kg to achieve a cumulative dose of 180 mg/kg over a period of 8 to 13 weeks.

Histopathological spectrum of childhood NS is variable in different geographic locations and variable response is reported with CPO in relapsing nephrotic syndrome as a group.[5] Due to our resource-limited setting and lack of national registry and database, there is a paucity of local data on the role of CPO in relapsing SSNS. This study was undertaken to estimate the duration of sustained remission after a completed CPO course in children with relapsing SSNS with different histopathological lesions, and the common complications encountered in patients receiving this treatment regimen. The results would assist in predicting the prognosis for children with relapsing SSNS treated with CPO and establishing the efficacy of CPO in this patient group.

METHODOLOGY

All children who underwent renal biopsy for relapsing SSNS from the year 2012 to 2014 were included. All the patients received a minimum of two years follow-up. Infantile NS, adolescent NS, children with prior use of non-steroidal immunosuppression and those who were

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lost to follow-up during treatment were excluded from the study. Relapsing SSNS was defined as >2 relapses in a year.[6]

Duration of NS, treatment with CPO and sustained remission post-CPO were recorded. Immediate and long-term side effects were documented. Our treatment protocol for relapsing SSNS include Cyclophosphamide cumulative dose 180 mg/kg (daily dose 2 - 2.5 mg/kg) and Prednisolone 1 mg/kg every other day. Patients presenting with first episode of NS were treated with longer duration of therapy in accordance with the recommendations of Cochrane meta-analysis.[7]

Data on all the children fulfilling the inclusion criteria were retrieved and recorded. SPSS 20 was used for statistical analysis. Quantitative variables with non normal distribution of data were expressed as median with interquartile ranges of 25 to 75; those with normal distribution were expressed as mean and standard deviation. Categorical variables were analysed with frequencies and percentages.

RESULTS

The demographic data revealed a male predominance (Table I). Out of the total 74 patients, there were 47 (63.5%) boys and 27 (36.5%) girls. Median age (Interquartile range) at presentation was 5 years (4-7 years). Minimal change disease (MCD) was the most common histopathological diagnosis recorded in 54 (73%) children, followed by focal segmental glomerulosclerosis (FSGS) in 13 (17.5%). MesPGN was diagnosed in six (8.1%) children, while one patient (1.4%) had IgA nephropathy. Each biopsy sample had a median of 15 (11-21) glomeruli and the median duration of treatment was 11 weeks (9-13 weeks). A median timeframe of 17 months (13-24.2 months) lapsed between establishing the diagnosis of NS and initiation of treatment.

Table I: Demographic and baseline characteristics.

Median age	5 years (4-7)
Median weight	20 Kg (16-25)
Male : Female	1.7 : 1
Median total glomeruli in renal biopsy	15 (11 - 21)
Median duration of CPO treatment	11 Weeks (9 - 13)
Median remission post-CPO therapy	13 Months (7 - 23)
Median nephrotic syndrome duration pre-CPO therapy	17 Months (13 - 24.2)

Table II: Short-term outcome of cyclophosphamide.

End of CPO therapy	
Complete remission	72 (97.3 %)
CNI dependant	2 (2.7%)
CKD	0 (00%)
Follow-up at 1-year	
Complete remission	41 (55.4 %)
CNI dependant	32 (43.2%)
CKD	1 (1.4%)
Follow-up at 2-year	
Complete remission	27 (36.5%)
CNI dependant	45 (60.8 %)
CKD	2 (2.7 %)

CPO = Cyclophosphamide; CKD = Chronic kidney disease.

Complete remission was achieved in 72 (97.3%) patients at the end of therapy (Table II). At one year follow-up, 41 (55.5%) were still in remission while at two years follow-up, 27 (36.5%) patients remained in complete remission. The median duration of complete remission was 13 months (7-23 months).

Those patients who continued to have relapses of NS after CPO therapy were treated with calcineurin inhibitors (CNI). The number of these children at the end of therapy, at one year and two years post-CPO treatment were 2 (2.7%), 32 (43.2%) and 45 (60.8%), respectively. Only two (2.7%) patients progressed to chronic kidney disease (CKD) at the end of follow-up.

Leucopenia was the most common complication affecting six (8.1%) patients. CPO was held while steroids were continued. Close follow-up of these patients was maintained and treatment was resumed once WBC count was more than 4000 cells/ul. All the patients who had developed leucopenia recovered completely on holding CPO and completed their course. Anemia and alopecia were encountered in one patient each; which reversed spontaneously after the cessation of therapy.

Table III summarizes the details of response to CPO treatment based on histopathological diagnoses. MCD was found in 54 (73%) patients out of which 33 (61%) were males and 21 (39%) were females. Median age at presentation was 5 (4-7) years and the duration of treatment was 11 (9-13) weeks. After the diagnosis of NS, it took 17 (13-27) months to establish the diagnosis of relapsing nature and after the treatment sustained remission was observed for a median of 12 (5.5-22) months.

FSGS was diagnosed in 13 (17.5%) patients of whom 8 (61.5%) were males and 5 (38.4%) were females. Mean age of presentation was 6.6 ±2.4 (4-11) years. On an average 16.6 ±4.9 (8-28) months lapsed between diagnosis and commencing treatment while treatment lasted for 11.1 ±2.3 (8-12) weeks. Sustained remission was observed for 20.4 ± 8.4 (9-33) months.

Table III: Outcome of cyclophosphamide.

	Number of patients n (%)	Male : female (M:F)	Median/mean age (years)	Median /mean duration of CPO therapy (weeks)	Median/mean duration of remission (months)	Median/mean duration of NS
MCD	54 (73 %)	1.5:1	5 (4 - 7)	11 (9 - 13)	12 (5.5-22)	17 (13 - 27)
FSGS	13 (17.6%)	1.6:1	6.6 ±2.4	11.1 ±2.3	20.4 ±8.4	16.6 ±4.9
MesPGN	6 (8.1%)	5:1	6 (5-11)	12.1 ±1.7	15.6 ±9.8	15.6 ±6.6

FSGS = Focal segmental glomerulosclerosis; MCD = Minimal change disease; MesPGN = Mesangioproliferative glomerulonephritis.

MesPGN was the biopsy proven diagnosis in 8% patients. All of them were males except one with a median age at presentation of six (5-11) years. CPO was given for a mean duration of 12.1 ±1.7 weeks with minimum of 9 weeks and maximum of 14 weeks. The mean duration of NS prior to starting CPO therapy was 15.6 ±6.6 (9-23) months whereas the mean duration of sustained remission was 15.6 ±9.8 months with minimum nine months and maximum 23 months.

DISCUSSION

This is a descriptive, observational single-centre analysis conducted on patients treated with CPO for relapsing SSNS from 2012 till 2014. At the study centre, patients presenting with the first episode of NS are treated with longer duration of steroid therapy. Hence, it is difficult for us to define relapsing NS as a separate entity.[7-12] None of the patients had received any other immuno-suppressant other than steroids prior to CPO. Therefore, the sustained remission can only be attributed to CPO treatment. The exact duration of treatment with CPO for SDNS is not mentioned in literature. Ueda *et al*. and APN study CYTO II concluded that > 8 weeks therapy with CPO is recommended.[13,14] Later, similar results were replicated by Garin *et al*. and were also supported by KDIGO guidelines.[15,16] There is no controlled trial to assess if the response to treatment differs with the dose of CPO or the duration of treatment.

The time duration to first relapse is of paramount importance in predicting the efficacy of the applied treatment protocol. The present data revealed a median of 13 months' time to relapse while 55.4% and 36.5% of patients were in complete remission at one year and two years post-treatment, respectively. Takeda *et al*. reported a lower percentage (42.9%) in complete remission at one year post-CPO, while the remission rate was higher in patients treated with Chlorambucil (70%) and Cyclosporine A (79%).[17] Karilesis *et al*. reported a complete remission rate of 35% post-CPO at two years,[18] which is comparable to the present result. Kemper claimed sustained remission in 30% of subjects at two years when treated with CPO at a dose of 2 mg/kg.[19] A similar study conducted in France recorded post-CPO remission in 57% of patients at one year, 42% at two years and 31% at five years.[20]

Azib *et al*. reported seven months as the median time to relapse post-CPO and 14 months post-Rituximab.[21] The median time to relapse in our patient group was 13 months which is comparable to 14 months post-Rituximab as documented by Azib *et al*.[21]

Furthermore, our data reported relapsing SSNS pattern to be consistent with FSGS in 13 children, 61% of whom had complete remission at two years post-CPO. Similar results were published by Lanewala *et al.* showing 69% of children with FSGS histology achieving complete remission.[22] Another study on primary FSGS from Brazil established a lower percentage (26.7%) of children in complete remission and further lower (20%) in partial remission.[23] Sustained remission post-CPO for FSGS was 20.4 months which is greater than other histo-pathological variants, i.e. MCD (12 months) and MesPGN (15.6 months).

The use of slightly higher doses for CPO (cumulative dose: 180 mg/kg) and steroids (1 mg/Kg /day EOD) can possibly explain the prolonged remission in our patients. A glance at the common CPO complications encountered in our subset of patients reveal comparable results with those reported in literature. All the reported adverse effects were reversible upon cessation of CPO treatment.

CONCLUSION

Improved short-term outcome for relapsing SSNS were achieved using CPO and steroids in the studied subset of patients. There were minimal reversible short-term side effects. Since these results were based on a single-centre experience without controls, a large scale multicentre-controlled trial is required to further validate these results.

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ORIGINAL ARTICLE

Diagnostic Accuracy of Risk of Ovarian Malignancy Algorithm (ROMA) in Post-Menopausal Patients with Ovarian Mass

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Abstract

Objective: To determine the diagnostic accuracy of ROMA in postmenopausal women with history of ovarian mass.
Study Design: Observational study.
Place and Duration of Study: Dr. Ziauddin University Hospital, Karachi, from May 2014 to June 2015.
Methodology: Two hundred and sixty postmenopausal women of 40-65 years of age with ovarian masses, planned for surgery, were included in the study. Their samples were obtained preoperatively and analysed on Abbot Architect i1000 SR immunoassay analyser for quantitative estimation of tumor markers, i.e. HE4 and CA125. By combination of these two tumor markers, ROMA scores were calculated and studied after histopathological verification of masses.
Results: Total number of patients were 260, out of which 122 (46.9%) were diagnosed as having ovarian cancer, while 138 (53.0%) were diagnosed as benign condition. Median ROMA score levels in patients with malignant masses were 95.58 (IQR=44.4) as compared to 20.6 (IQR=14) in benign masses. ROMA had sensitivity 92.6% (CI=86.47-96.04), specificity 78.3% (CI=70.09-83.82), positive predictive value 79% (CI=70.87-84.29), negative predictive value 92.3% (CI=86.02-95.9) and positive likelihood ratio 4.26, while negative likelihood ratio 0.1. Diagnostic accuracy of ROMA was 85%, based on ROC curve analysis. ROMA had the highest sensitivity in detecting ovarian carcinoma.
Conclusion: ROMA is a very useful diagnostic tool for the preoperative stratification of patients with ovarian masses showing 85% diagnostic accuracy. However, there is need of more studies with homogenous laboratory procedures for HE4 and CA125 assays as well as patients, selection criteria, so we can draw firm conclusion about utility of ROMA in clinical setups.

Key Words: *Diagnostic accuracy. ROMA. Post-menopausal. Ovarian mass. HE4. Tumor markers.*

INTRODUCTION

Ovarian cancer is a common and fatal gynecological malignancy with high morbidity and mortality rates. Ovarian cancer is the second most common cancer among women accounting 13.6% female malignancy.[1] Both vague symptoms and location cause ovarian cancer to be diagnosed in advance stages.[2] The long term survival rate is <30% in advance stages while 5 years survival rate exceeds 90% in localised tumors. Unfortunately, only <20% of ovarian cancers are localised to the ovaries at the time of diagnosis.[3] Current practices for the diagnosis of ovarian masses are trans-vaginal ultrasounds and other imaging techniques. Serum biomarkers like CA 125 and HE4, histopathology and proteomics are also available. Suspicion of malignancy is based largely on imaging appearance and experience of physician for distinguishing benign from malignant.[4] The accuracy of ultrasonography is still low for detecting ovarian cancer and highly false positive rates have been reported by using other imaging technologies.[5] In comparison with histopathology, which is taken as gold standard for the diagnosis and also an invasive procedure, serum tumor markers are rather cost-effective, non-subjective, and non-invasive technique.

Nowadays, among several tumor markers, CA 125 is being used for the diagnosis of ovarian cancer but CA 125 levels may also be raised in other benign reproductive disorders like endometriosis, benign ovarian cysts, first trimester of pregnancy and pelvic inflammatory diseases, fibromas, dermoid cysts etc. New tumor markers are also emerging and in combination with CA 125, they can improve the specificity for diagnosis. HE4 (Human Epididymis Protein 4) is a new tumor marker and has been proposed for ovarian cancers as it is frequently over-expressed in ovarian cancers and its levels are less likely to be elevated in benign conditions as is the case with CA125.[6]

Risk of ovarian malignancy algorithm (ROMA) is a scoring system based in corporation of CA-125 and HE 4 with menopausal status and shows excellent diagnostic performance for the differentiation of ovarian cancers from benign masses. ROMA stratifies these patients into high risk group or low risk group.[7] This stratification of risk of having malignancy is becoming important when laparoscopy or non-invasive management is being considered in benign cases or very extensive cyto-reductive surgeries are being mandatory by gynecologic oncologist.[5,7,8]

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The objective of the study was to determine the diagnostic accuracy of risk of ovarian malignancy algorithm (ROMA) in our population, as there is no data available in Pakistan as well as there are limited studies which show discrepancy regarding diagnostic accuracy of ROMA.

METHODOLOGY

This observational study was conducted from May 2014 to June 2015 in the Department of Chemical Pathology, Dr. Ziauddin University Hospital. Two hundred and sixty postmenopausal women with ovarian mass (>2 cm) on pelvic ultra sound examination, attending gynecology clinics, planned for surgical intervention, were informed about the study and consent was taken for participation in it. Permission from the Ethical Committee of the Hospital was taken. Questionnaire was filled. Menopausal status was determined by history of the patients and age group, as inclusion criteria. Those who did not give consent were excluded from the study.

Blood samples were collected from all the patients into the serum separator tube, before their surgical procedures, and centrifuged at 4000g for 15 minutes then part of the sample was transferred to aliquot and stored at -30° centigrade until testing. Serums were analysed for the quantification of CA125 and HE4 on automated immunoassay analyser, Abbot ARCHITECT i1000 by chemiluminescent microparticle immunoassay method. All manufacturer recommendations for maintenance, calibration, and internal quality assessment were followed for both assays.

ROMA was calculated using CA 125 and HE4 results by using ROMA calculator, which is based on predictive index. Predictive index was calculated from the equation; post-menopause PI = -8.09 + 1.04*LN (HE4) + 0.732*LN (CA125),[9] where LN is the natural logarithm. ROMA was determined using the equation: ROMA (%)= exp (PI)/[1-exp (PI)]*100.[10]

A score of 27.7% was adopted as the cutoff point for ROMA as recommended for postmenopausal patient.[7] The patients were labelled as either malignant or benign, according to histopathological findings. Accuracy of the ROMA was assessed by measuring specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV). Confounding variables were controlled by strictly following the inclusion and exclusion criteria.

Median with interquartile values were calculated for quantitative variables like age, size, CA125 and HE4 levels; while frequencies with percentage were calculated for qualitative variables. HE4, CA125, and ROMA represented diagnostic variables acting as stimulants which increase the probability of ovarian cancer proportionally to their rising value. Asymmetrically (skewed) distributed quantitative variables were compared by Mann-Whitney test for two disease groups. Effect modifiers like age, and size of the tumor were controlled by stratification. Diagnostic accuracy was represented in terms of sensitivity, specificity, positive predictive value and negative predictive value, and positive and negative likelihood ratio derived from contingency table to evaluate the diagnostic performance of ROMA. ROC curve analysis and 95% CI was used to validate the ROMA performance, while p-value less than 0.05 was taken as significant. All analyses were performed on SPSS version 20.

RESULTS

A total of 260 postmenopausal women, diagnosed for having ovarian mass on ultrasound were included in this study. The average age of the patients was 49.28 ±6.26 years. The mean size of tumors, CA125 and HE4, are given in Table I. Standard cutoff values for HE4, and CA125 were already established, i.e. 150 pmol/L and 35 U/L, respectively. The most common benign tumor was serous cyst adenomas which accounted for 30% (n=42), followed by mucinous cyst adenomas which accounted for 21% (n=29). Dermoid cysts were 18% (n=25), followed by endometritic cysts and stromal cell tumor (10%, n=14 each); while 11.6% (n=16) were of other category. Of malignancies, there were 51% (n=62) endometioid carcinoma, 30% (n=37) serous cyst carcinoma, 7.3% (n=9) clear cell carcinoma, 4% (n=5) mixed epithelial tumor and mucinous adenocarcinoma 2% (n=3), 5% (n=6) papillary carcinoma.

The median serum levels for CA125 was 49.45 IU/ml (IQR=761.5) while HE4 median level was 101.55 pmol/L (IQR=456.3) as shown in Table I. CA125 and HE4 levels were significantly high in ovarian malignancies. CA125 and HE4 median levels were 685.7 (IQR=2605.3) IU/ml and 543.9 (IQR=1256) pmol/L, respectively as compared to benign disorders where CA125 and HE4 median levels were 25 (IQR=43.9) IU/ml and 57 (IQR=41) pmol/L, respectively ($p<0.001$). CA125 levels were markedly increased in fibromas and some dermoid cysts. HE4 levels were not falsely elevated in these conditions. ROMA median levels in patients with malignant masses were 95.58 (IQR=44.4) as compared to 20.6 (IQR=14) in benign masses ($p<0.001$).

ROMA score was elevated in 113 out of 122 ovarian cancer patients, while not elevated in108 out of 138 benign cases as shown in Table II. Sensitivity, specificity, PPV, NPV and diagnostic accuracy of ROMA in detection of ovarian tumors in postmenopausal women was very good as shown in Table II.

The best cutoff point was 28.11%. AUC for ROMA was 91.4% at sensitivity 92.6% and specificity 78.3%, which was higher as compared to CA125 alone, as shown in Figure 1.

Stratification analysis was performed and observed that accuracy of ROMA in detection of ovarian tumors in

postmenopausal women was above 80% in all age groups; except in 56 to 60 years of age, accuracy was 79.3% as shown in Table III. Similarly, with respect to tumor size, accuracy of ROMA was about 91% in cases where size of tumor was 3 to 10 cm and above 15 cm while 67.65% in cases where tumor size was 11 to 15 cm as shown in Table IV.

Table I: Descriptive statistics of the patients.

	95% Confidence Interval for Mean		Median	IQR
	Lower bound	Upper bound		
Age (years)	48.47	50.09	48	11
Size of tumor (cm)	8.53	9.65	8	6
CA125 IU/ml	765.6	1317.15	49.45	761.5
HE4 pmol/L	372.11	669.86	101.55	456.3

Table II: Diagnostic accuracy of ROMA in detection of ovarian tumors in postmenopausal women taking histopathology as gold standard (n=260).

ROMA	Histopathology		Total
	Malignant	Benign	
ROMA value >27.7% [Malignant]	113 (TP)	30 (FP)	143 (55%)
ROMA value <27.7% [Benign]	9 (FN)	108 (TN)	117 (45%)
Total	122 (46.5%)	138 (53.5%)	260
Sensitivity	=113/122	=92.6%	
Specificity	=108/138	=78.3%	
PPV	=113/143	=79.0%	
NPV	=108/117	=92.3%	

Positive likelihood ratio = 4.26; Negative likelihood ratio = 0.1; Accuracy = 85%.

Table III: Diagnostic accuracy of ROMA in detection of ovarian tumors in postmenopausal women taking histopathology as gold standard in respect to age of patient.

	40-45 n=108	46-50 n=51	51-55 n=38	56-60 n=63
True positive	25	25	25	38
False positive	10	7	3	10
False negative	2	2	2	3
True negative	71	17	8	12
Sensitivity	92.6%	92.6%	92.59%	92.7%
Specificity	87.7%	70.8%	72.73%	54.5%
PPV	71.4%	78.1%	89.2%	79.17%
NPV	97.3%	89.5%	80%	80%
Diagnostic accuracy	88.9%	82.3%	86.84%	79.37%

Table IV: Diagnostic accuracy of ROMA in detection of ovarian tumors in postmenopausal women taking histopathology as gold standard in respect to tumor size.

	Size of the tumor		
	3 to 10 cm n=169	11 to 15 cm n=69	>15 cm n=22
True positive	62	37	14
False positive	8	21	1
False negative	7	1	1
True negative	93	9	6
Sensitivity	89.7%	97.4%	93.3%
Specificity	92.1%	30%	85.7%
PPV	88.4%	63.79%	93.3%
NPV	93%	90%	85.7%
Diagnostic accuracy	91.1%	67.65%	90.9%

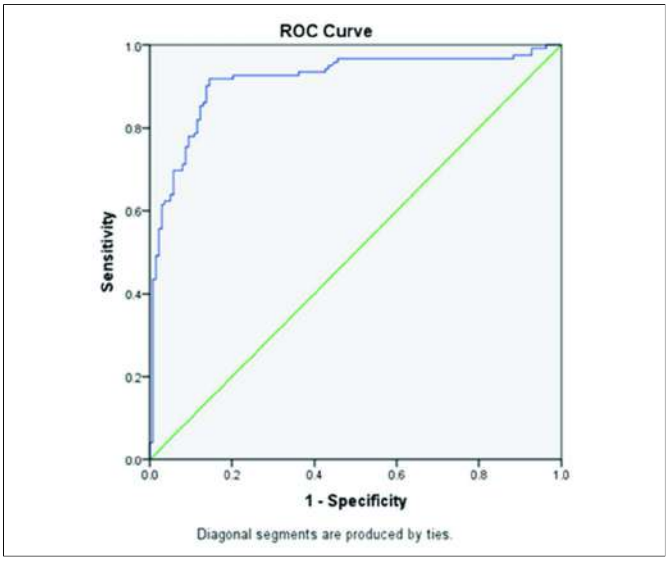

Figure 1: ROC-AUC analysis of ROMA.

DISCUSSION

Ovarian cancer is the most frequent cause of death from gynecological cancer. It has highest fatality ratio of all gynecological malignancies, which is characterised by the early widespread metastasis and high grade malignancy at the time of diagnosis.[11]

Studies are being available since many years for a novel, more sensitive, and more specific tumor marker or diagnostic algorithm to provide the stratification of patients with a pelvic mass and for screening in ovarian cancer.[12,13] Much hope has been attached recently to the ROMA algorithm, developed by Moore *et al*.[9] By combining serum CA125 with HE4 levels and menopausal status of patients, ROMA was considered helpful as it reduces the number of false positive cases with elevated CA125.[14,15] Some studies have claimed superiority of ROMA over other biomarkers of ovarian malignancies and algorithms; but also suggested that further studies are also required to prove their claim.[16]

Total number of patients selected in this study were 260; out of which, 46.9% were diagnosed as having ovarian cancer both clinically as well as proven histopathologically. In this study, there was a significant difference between benign and malignant disease with respect to serum CA125, HE4 and ROMA levels. ROMA was sensitive and specific marker as our results were consistent with other studies.[17] Studies conducted by Hellstrom *et al*. in 2003 and Montagnana *et al*. in 2009 showed similar performances of CA125, HE4 and ROMA.[8,18]

In this study, ROMA misclassified 22.3% benign tumors and showed high risk for malignancy, i.e. false positivity among stromal cell tumors like fibromas and adenofibromas, which showed its lack of specificity in non-epithelial tumors when compared with endometriotic cyst, and dermoid cyst; while 78.3% were classified as true negative, i.e. low risk for malignancy in serous and

mucinous cyst adenomas. Among malignant tumors, ROMA misclassified 7.43% cases as falsely negative, although by histopathology they were malignant. ROMA score were significantly high in epithelial ovarian cancers rather than in non-epithelial tumors. These results were consistent with the study performed by T Van Gorp *et al*. which showed elevated ROMA values in fibroma / thecomas and cystadenofibromas.[19]

The high negative predictive value in this study provides a strong reassurance that a pelvic mass is benign. The sensitivity, specificity, PPV, NPV values and accuracy of ROMA were consistent with other studies.[13,17,20] A study, conducted by Moore, concluded that dual marker combination successfully classify pelvic mass into benign and malignant as shown in our study.[9] By using area under the receiver operator characteristic curves analysis (AUC ROC) as a measure of test performance, among CA125, HE4 and ROMA, ROMA achieved a higher AUC ROC (0.914, CI=0.876-0.952, p <0.05), and therefore, had increased sensitivity than either marker alone. These findings also validate the performance of ROMA.

In 2009, FDA approved ROMA and recommended its use in women over 18 years of age with a pelvic tumor or cyst qualified for surgery, emphasizing that ROMA must always be interpreted against clinical and radiological findings. ROMA is a very useful diagnostic tool for stratification of patients with a pelvic mass.[14]

Several multinational studies were published on validation of ROMA for ovarian mass risk stratification. When combined these studies, which performed in the United States, Europe and Asia over 4,000 women with ovarian mass, the range of sensitivity for ROMA test was found from 75% - 94%, at specificity from 75% - 95%. As in this study, ROMA demonstrates consistent and reliable performance for classifying ovarian mass into high risk and low likelihood groups for epithelial ovarian cancers. ROMA may help physicians in identifying as well as triage women to specialising unit in the care and management of ovarian cancer.[7,21]

Limitations of this study were absence of multicenter data collection and also lack of availability of comorbidity data. However, strengths are that sample size was appropriate and very few studies have been conducted on ROMA in our part of the world.

CONCLUSION

It is concluded from this study that ROMA is a very useful diagnostic tool for the preoperative stratification of patients with ovarian mass showing 85% diagnostic accuracy, as the combination of CA125 and HE4 gives better differentiation between benign and malignant lesions as compared to being used alone.

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ORIGINAL ARTICLE

Radiotherapy Outcome for Pediatric Pelvic Ewing Sarcoma

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ABSTRACT

Objective: To evaluate the outcomes of patients undergoing radiotherapy for primary local control of pelvic ewing sarcoma (ES).

Study Design: Case series.

Place and Duration of Study: Shaukat Khanum Memorial Cancer Hospital, Lahore, from January 2010 to October 2015.

Methodology: Patients with primary pelvic ES were included in the analysis and all other primary disease sites were excluded. All of them were treated with radiotherapy and followed the EuroEwing-99 chemotherapy protocol. Tumor volume, relapse and metastases were noted.

Results: There were 13 patients with pelvic ES. The median age at the time of diagnosis was 15 years with IQR of 7 years (range 2-19 years). Tumor volume was more than 400ml in more than 50% of the patients. Eight patients (61.5%) had local relapses and 5 patients (38.5%) had combined local and distant disease metastases.

Conclusion: These results showed poor local control and overall survival in local pelvic ES cases in children and adolescents. Intensity modulated radiotherapy (IMRT) can be used to deliver higher doses of radiation. Compressed cycles of chemotherapy should be evaluated in local setting.

Key Words: *Pelvic ewing sarcoma. Tumor volume. Radiation therapy. Paediatrics.*

INTRODUCTION

Ewing sarcoma (ES) is the second most common bone tumor in children and adolescents.[1] The estimated incidence in White children less than 15 years of age is about 2.8 per million.[2] Pelvis is a common site of disease seen in about 25% patients of ES. This site is also seen to be associated with other factors such as large tumor volume and higher frequency of metastases that can lead to worse outcomes in these patients.[3-5]

Modern intensified systemic chemotherapy regimens has led to 5-year overall survival (OS) rate of more than 80% in localised disease.[6] Multimodality therapy has been critical in improving the outcomes of patients with ES. Local control with surgery or radiation, or both, is essential for cure. The challenge with pelvic ES is the anatomy. The ability to achieve local control with surgery without damaging vital structures such as bowel, vessels, and nerves is difficult.[7] Radiation therapy is commonly used for primary local control in such cases.

Long-term overall survival for patients with localised pelvic ES, treated with radiation, is about 50-70%.[8,9] Most failures in this group of patients is due to local relapse which can be more than 20%.[2]

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In this study, the aim was to evaluate the treatment of localised pelvic ES in children and adolescents, the local control modalities used, and the overall outcomes of these patients.

METHODOLOGY

This retrospective case series analysis was conducted at the Shaukat Khanum Memorial Cancer Hospital in Lahore, Pakistan. Institutional review board (IRB) authorised the study. Records were reviewed to identify patients diagnosed with ES between January 2010 and October 2015. Patients with pelvic primary site were included for the analysis and the rest of disease sites were excluded. Data was collected on patients' disease site, tumor volume, radiation dose administered, systemic therapy, and relapse site.

All patients were treated as per the EuroEwing-99 (EE-99) chemotherapy guidelines. Treatment included six courses of induction chemotherapy with vincristine, ifosphamide, doxorubicin and etoposide (VIDE). Local control was performed after 6 courses of VIDE and the interim scans. Surgical option was considered in multi-disciplinary team meetings (MDTMs), if resection was possible without local neurovascular or sphincter damage, lack of disease progression; and most importantly, patient consent. Radiation therapy was given on-site at the hospital after computed-tomography (CT) simulation. The radiation-oncology team carried out radiation planning and administration.

Tumor volume (TV) was calculated as per the formula utilized in the EuroEwing-99 regimen a*b*c*0.52 for spherical and a*b*c*0.785 for cylindrical tumors. Patients not eligible for surgical local control were offered radiation therapy. Consolidation was eight

courses of vincristine, actinomycin-D and ifosphamide (VAI) that started during local control. Excel software was used for data collection and calculation of frequencies with percentages (%) for categorical variables, median with interquartile ranges (IQRs) for non-parametric continuous variables, and mean ± standard deviation (SD) for radiation doses.

RESULTS

During 2010 to 2015, 129 patients (n=129) with ES were treated at our institution. Among those, 13 had pelvic primaries. Only one patient got diagnosed using the EWSR-1 translocation since the test was launched in October 2015. The median age at the time of diagnosis was 15 years with IQR of 7 years (range 2-19 years). The median follow-up was 20 months with IQR of 8 months (range 13-64 months). About 27% of pelvic tumors (n=10) were non-metastatic at diagnosis.

Patient disease characteristics are shown in Table I. Three of these patients had outside films at baseline that could not be accessed at the time of this analysis for calculation of tumor volumes. The tumor volume at diagnosis was more than 400ml in seven patients (53.8%). All patients received chemotherapy as per the EE-99 protocol. Interim scans were discussed in MDTMs. Patients with sacral involvement were not deemed to be surgical candidates. Nine (69.2%) patients had non-sacral involvement. These patients were not offered hemipelvectomy due to the extensive nature of their disease and the non-availability of the necessary supportive and operative care infrastructure.

Table I: Patient disease characteristics.

	Number of patients (%)
	13 (100%)
Gender	
Male	7 (53.8%)
Female	6 (46.2%)
Age	
<10 years	2 (15.4%)
>10 years	11 (84.6%)
Disease stage	
Metastatic	3 (23.1%)
Non-metastatic	10 (76.9%)
Tumor volume	
<400ml	3 (23.1%)
>400ml	7 (53.8%)
Unknown	3 (23.1%)
Tumor location	
Sacral	4 (30.8%)
Non-sacral	9 (69.2%)
Local control	
Surgery	0
Radiation	13 (100%)
Surgery and radiation	10 (76.9%)
Chemotherapy	
VIDE	13 (100%)
Outcomes	
Alive (DNR)	3 (23.1%)
Dead	10 (76.9%)

Table II: Radiation details.

	Number of patients (%)
Definitive radiation dose	
< 54 Gy	8 (61.5%)
>/= 54 Gy	5 (38.5%)
Delay in planned radiation	
Yes	9 (69.2%)
No	4 (30.8%)
Sites of metastases	
Lung	0
Bone	3 (23.1%)
Radiation of metastatic sites	
Yes	13 (100%)
No	0
Relapse pattern	
Local only	8 (61.5%)
Distant only	0
Combined	5 (38.5%)

The mean radiation dose was 50 Gy (range 45-55.8 Gy) with 50 Gy ±4.4 Gy of standard deviation. All of the five patients who got doses more than 54 Gy (Table II) had a delay in the planned duration of therapy. Four (80%) of the five patients, treated with radiation dose of more than 54 Gy, had tumor volume of less than 1000 ml. One patient's tumor volume was missed because her baseline scan, done at an outside facility, was not available at the time of this analysis.

Three (23%) of these patients are still alive at the time of this review, but under palliative care. None of the patients made it to 5 years without having a relapse. Eight patients (61.5%) had local relapses, while the rest of the five patients (38.5%) had combined local disease progression as well as distant metastases.

DISCUSSION

Pelvic tumors have historically been associated with a grim prognosis as compared to non-pelvic tumors.[10,11] Combined therapy with multi-agent chemotherapy, surgery and/or radiation is key in the treatment of Ewing sarcoma. Existing literature shows that local therapy of Ewing's sarcoma is critical not only for local disease control but also overall survival.[12,13]

Surgery is preferred in children if the tumor is small, peripheral, and localised. Radiation therapy is chosen for local control when the tumor is axial and larger in size. Akagunduz *et al*. showed radiotherapy (RT) either alone or as an adjuvant to surgery, provided local control in about 80% of non-extremity Ewing sarcomas.[14] Local control can remain challenging with about 20%-30% incidence of local failure.[9,13,15,16]

These results showed poor local control and overall survival. Statistical analysis was not feasible and meaningful due to the small number of patients. The local failure rate was more than 50% in patients who were non-metastatic. Thirty percent of these patients had sacral tumor that was not amenable to surgery. The rest of the 60% were large volume tumors; and hence, were not operated on because of lack of expertise and supportive care facilities in the study centre set-up.

Radiation doses also vary among centers depending on patient characteristics. Low-dose radiation has been used for pediatric patients with small tumor size and good chemo response.[2,17] A recent study from St. Jude showed that dose escalation up to 64.8 Gy showed favourable local control.[18] Twelve children (92.3%) got radiation doses between 40-54 Gy. There was only one child who got a dose of 55.8 Gy.

A significant number of patients faced delay in planned RT. This was mostly due to infrastructure issues, such as increasing patient numbers, lack of other referral centers in case of mechanical problems. It is essential that we minimise the delay in RT planning and delivery. RT dose intensification in the pelvis as per reported literature can be challenging due to gastrointestinal dose-limiting toxicity. All these patients were planned with 3D CT conformal planning, but not with intensity modulated radiotherapy (IMRT). Therefore, doses beyond 45 Gy could not be delivered safely in the majority cases due to small bowel dose constraints. With the availability of IMRT this year (2017) at our centre, we now hope to be able to escalate radiation dose in such patients, which has a prospective to improve local control.

The latest children oncology group (COG) trial, AEWS0031, showed a 5-year OS of 77-83% and EFS of 65-73% with the interval compressed chemo regimen.[6] All these patients were treated on the EE-99 protocol, which is given every 21-days. Systemic therapy tends to influence local control.[2] The possibility of improving local disease response with switching to interval compressed chemo regimen, such as AEWS0031 which is given every 14-days, should be evaluated in our patient setting. Our pediatric population in general is malnourished and cachectic with compromised immune systems. We would then need to study how well they tolerate the compressed cycle chemotherapy regimens along with the disease outcomes.

CONCLUSION

This single-institution retrospective study of a small cohort of patients with pelvic ES showed that despite good survival outcomes in pelvic ES in the current era, the results are still dismal. There is a need for intensifying both systemic therapy and radiotherapy in a judicious manner.

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ORIGINAL ARTICLE

Serum Oxidative Stress Markers in Patients with Senile Cataract and Healthy Controls

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Abstract

Objective: To investigate the role of oxidative stress in patients with senile cataract.
Study Design: Case-control study.
Place and Duration of Study: North Khorasan University of Medical Sciences, Bojnurd, Iran, from 2014 to 2015.
Methodology: Non-randomised sampling was conducted on 74 patients with senile cataract and 79 healthy people. The oxidative stress level, glutathione peroxidase (GPx) and superoxide dismutase (SOD) enzymes were measured in serum. The results were analysed using SPSS software and followed by t-test analysis. P<0.05 was considered to be significant.
Results: The median activity of GPx and SOD antioxidant enzymes in patients with cataract, was higher than healthy people (p=0.018 and p<0.0001, respectively). Peroxide-antioxidant (PAB) levels in patients with cataract was significantly higher than in healthy people (p<0.0001).
Conclusion: This study showed that despite the high level of oxidative stress in patients, the activity rate of GPx and SOD enzymes also increased.

Key Words: *Cataract. Glutathione peroxidase. Superoxide dismutase. Oxidative stress.*

INTRODUCTION

Cataract is clouding or opacity of the eye lens, which is the main cause of blindness.[1] A recent report by the World Health Organization (WHO) showed that 47.8 percent of blindness cases are caused by cataract.[2] Seventeen percent (20.5 million) of Americans over 40 years are suffering from cataract and it may increase to more than 30 million by 2020.[3] The exact statistics are not available regarding the prevalence of cataract in Iran, but it seems that one-fifth of the population over 40 years are suffering from cataract in the country.[4]

Cataract is a multifactorial disease. Risk factors, such as aging, high blood glucose levels, exposure to ultraviolet radiation, alcohol consumption, metabolic disorders, genetic factors, oxidative stress, and trauma are involved in cataract creation.[1,5] Although, age is not the only factor for cataract, but this disease is mainly related to age.[6] The research results showed that 82% of the population over the age of 50 years have cataract.[1]

Epidemiologic and experimental studies showed that oxidative stress is the main cause of initiation and progression of senile cataract.[1,2] Reactive oxygen species (ROS), which basically include molecules such as superoxide anion, hydrogen peroxide, and hydroxyl radicals were detoxified by enzymes such as glutathione peroxidase, superoxide dismutase, and catalase. In this way, the antioxidant system and the ROS remain in a state of homeostasis. When oxidative stress is induced by some external or internal factors, the homeostasis is disturbed and ROS will denatured many essential intracellular molecules such as nucleic acids, proteins, and lipids.[1]

As such, this study was done to evaluate the oxidative stress level and the antioxidant activity of serum GPx and SOD in patients with cataract.

METHODOLOGY

This is a case-control study conducted on 153 people who were referred to the Imam Ali Hospital with non-randomised sampling from 2014 to 2015. Of these, 74 patients, who were suffered from cataract with the confirmation of ophthalmologist, were stayed in the case group; and 79 patients, who were referred to the annual eye check-ups and had no cataract, stayed in the control group. The patients were matched in terms of age and gender. Cataract diagnosis was performed by an ophthalmologist under slit-lamp examination and other eye tests including Goldmann applanation tonometer, fundoscopy, retinoscopy, keratometry, etc. were done in

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order to rule out other eye disorders. All those people had impaired vision and their visual acuity was less than 3.10, and they had senile cataract at least in one of their eyes. They had no other ocular disorders that can justify reduction of their vision. Patients with secondary cataract as a result of diabetes, steroid use, and trauma were excluded from the research. The control group was in good health status and that was confirmed with their medical history in filling the related questionnaire and physiological experiments, and laboratory tests such as cholesterol, triglycerides, blood sugar, blood pressure and absence of disease related to the oxidative stress. None of the subjects have history of cardiovascular disease, liver disease, gastrointestinal or renal disorders. History of smoking, alcohol consumption, and external hormones intake was not observed in them.

The participants in the study were asked not to consume any vitamin supplements or carotenoid until the initiation of the experiments; whereas, tea and coffee intakes were limited in them. Their blood samples were collected for biochemical tests.

Venous blood (3 ml) was phlebotomised under sterile condition by disposable syringes after 12 hours of fasting. Samples were centrifuged for 15 seconds with temperature at 3500 rpm. Then, serum was separated and transferred to the clean tubes and stored in the freezing temperature of -70°C.

Measuring the enzymes activity is based on the spectrophotometric evaluation. Other tests and biochemical parameters such as blood glucose, triglycerides, cholesterol, etc. were measured using routine clinical biochemistry tests.

To assess the balance between oxidant and anti-oxidant (PAB), TMB (3,3',5,5' *Tetramethhylbenzidine*) and cation were used as a redox indicator (due to the electrochemical and optical properties). In this method, the oxidant and anti-oxidant balance was simultaneously measured in an experiment by two different reactions. In an enzymatic reaction, chromogenic TMB (color-causing) was oxidised by peroxidants to colored cation and in a chemical reaction, the TMB cation becomes colorless combination by antioxidants. Photometric absorption was compared with certain absorption of a series of standard solutions having different ratios (0-100%) of hydrogen peroxide and uric acid mixture.[7,8]

The measurement of the superoxide dismutase enzyme activity was performed using Ransod-Randox kit. Half ml of isolated RBC was washed 4 times with 3 ml of saline and then they were centrifuged for 10 minutes in the centrifuge device with the rate of 3000 rpm. The washed RBC was mixed with 2 ml of cold distilled water and kept at 4°C for 15 minutes. Obtained lysate was used to determine the SOD activity.

Measurement of the GPx enzyme activity was performed using Ransel-Randox kit. 0.5 ml of isolated RBC were diluted by 1ml of diluents and incubated for 5 minutes. This diluted substance was mixed with Drabkin's reagent and used to measure GPx.

Data are presented as mean ± SD or median (IQR), and frequencies with percentages to report qualitative variables. All experimental data in this study were statistically analysed with SPSS version 11.5. The normality of data checked by Kolmogorov-Smirnov test. The normal data evaluated by Student's t-test, and others were evaluated by Mann-Whitney test. Results were considered significant at $p < 0.05$.

RESULTS

Basic demographical and clinical characteristics of cataract and healthy groups were presented in Table I. Of the total 74 cases, 43 (58%) patients were females and 31 (42%) were males; and 79 individuals were in the control group, of which 45 (57%) were females and 34 (43%) were males. The median age (years) of patients was 65 (19) in the case study group; and was 63 (9) years in the control group. The studied people were matched in terms of age and gender. Cholesterol, triglycerides, glucose, systolic blood pressure, and diastolic blood pressure were measured. Among these factors, the cholesterol and triglycerides serum levels and diastolic blood pressure between two groups showed a significant difference ($p<0.0001$).

Table II compared prooxidant-antioxidant balance (PAB) in serum of cataract and non-cataract subjects. PAB was

Table I: Basic demographical and clinical characteristics of cataract and healthy patients. Data were presented as mean ± SD or median (IQR) and frequencies with percentages to report qualitative variables. All experiment data were analysed with SPSS 11.5. The normal data evaluated by Student's t-test, and others were evaluated by Mann-Whitney test. Results were considered significant at $p < 0.05$.

	Cataract group	Control group	P-value
Number (%)	74 (48%)	79 (52%)	
Age (years)	65 (19)	63 (9)	0.525
Sex(f/m)	43/31	45/34	
BMI (kg/m^2)	25.11±2.59	25.48±4.32	0.8
Cholesterol (mg/dl)	197.73±52.68	165.98±42.01	<0.0001
Triglycerides (mg/dl)	139 (127)	95 (51)	<0.0001
Glucose (mg/dl)	91 (28)	95 (22)	0.468
Systolic blood pressure (mmHg)	130 (20)	120 (20)	0.056
Diastolic blood pressure (mmHg)	80 (13)	70 (10)	<0.0001

Table II: Stress oxidative parameters in cataract and healthy patients. Data were presented as mean ± SD or median (IQR) and frequencies with percentages to report qualitative variables. All experimental data were analysed with SPSS 11.5. The normal data evaluated by Student's t-test, and others were evaluated by Mann-Whitney test. Results were considered significant at $p < 0.05$.

	Cataract group	Control group	P-value
PAB	74.66 ±27.9	44.01 ±20.40	p<0.0001
GPX (U/ml)	283.7 (102.3)	444.4 (322.4)	p=0.018
SOD (U/ml)	161.07 ±23.5	110.53 ±30.8	p<0.0001

49.01 ±20.90 in control group, and it was significantly increased in cataract patients (74.66 ±27.91 U/ml, p<0.001). Also, the GPx levels were 283.7 (102.3 U/ml) in control group and it was significantly increased in cataract patients 444.4 U/ml 322.4, p=0.018). The similar pattern also shown about SOD levels (U/ml); so, it was higher in cataract group than the control group, and its difference was significant (p<0.001, Table II).

DISCUSSION

The present study shows that oxidative stress, SOD and GPx levels significantly increased in serum of cataract patients. Until now, many studies have been done to evaluate the role of oxidative stress in the pathogenesis of age-related cataract. The results of measuring the activity of GPx and SOD in cataract patients are various in different researches.[9] Delcourt and colleagues examined the relationship between cataract and serum anti-oxidants. Their results showed the similar pattern like this study for SOD and GPx levels in patients compared to healthy controls.[10] Also, the erythrocyte SOD and GPx activity increased in one study, directed by Mohammadi, *et al*.[11]

Many researchers have postulated that diminished antioxidant activity in addition to elevated levels of free radicals plays a pivotal role in cataractogenesis in senile age group.[12,13] According to a study conducted by Kuar and colleagues on 50 patients of 45-75 years with cataract and 50 healthy subjects, demonstrated that lipid peroxidation products (MDA) in the serum of patients with cataract is higher than in healthy controls. SOD and GPx activity in patients with cataract decreased compared to healthy controls.[11] Chang *et al.*, also showed that the activities of SOD, GPx and Catalase (CAT) in cataract group were lower than those in the control group and the oxidative stress products malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), conjugated diene (CD), advanced oxidation protein products (AOPP), protein carbonyl (PC), and 8-hydroxydeoxyguanosine (8-OHdG) were significantly increased in serum in cataract patients.[1] Chandrasena and colleagues also showed that SOD and GPx activity in patients with cataract decreased compared to healthy controls.[14]

The controversy shown in different studies may be for some reasons. Studies indicate that natural antioxidants can act as prooxidants, which produce free radicals and cause DNA damage and mutagenesis.[15,16] For deletion of free radicals, different parts of antioxidants system including vitamins, antioxidants enzymes, and their cofactors are needed. If every antioxidant acts, it can produce prooxidant that will be omitted by next antioxidant cycle. Thus, a lack of each cycle can increase the prooxidants and the result will be oxidative stress. Because all antioxidants cycles cannot be evaluated, it seems that measuring total oxidative stress will be more effective.[17]

Oxidative stress is a term used to describe any challenge in which prooxidants predominate over antioxidants. It may be due to either increased production of ROS or decreased levels of antioxidants (enzymatic and non-enzymatic or both). Oxidative stress is thought to play a crucial role in the development of age related cataract.[18] Mechanistically, oxidative stress leads to increased production of ROS which in turn causes increased production of H_2O_2 in aqueous humour as well as in lens. H_2O_2 is several folds higher in aqueous humor of cataract patients. ROS and H_2O_2 damage proteins and nucleic acids and also can oxidize the sulphydryl groups. The redox setpoint changes rapidly upon initiation of oxidative stress and irreversible oxidative damage quickly develops.[19]

The lens defence system constitutes enzymatic anti-oxidants, that is, SOD, CAT, and GPx utilising superoxide and H_2O_2.[20,21] However, the SOD and GPx activity increased in current study, but it was shown in some other references that protective systems decrease with the age and long-term exposure to oxidative stress predispose lens cells at risk for cumulative oxidative damage and cataract formation.[22] Higher systemic oxidative stress increases the risk of developing age-related cataract.[23] The effectiveness of SOD and other antioxidant enzymes is limited to several reasons such as their deactivation with aging. Being macromolecules, they cannot penetrate the certain sensitive sites of oxidation in nucleic acids and in proteins. The lens is surrounded by aqueous and the vitreous humors, fluids which lack the enzymatic defences. Therefore, the lens cell membranes, which are continuously exposed to a photochemical oxidative environment due to the continued light penetration during the long periods of photopic vision, remain susceptible to photo damage.[24,25]

Although this research was carefully carried out, but, we are still aware of its limitations and shortcomings. First of all, the research was conducted in senile cataract only. Second, the sample size was small.

CONCLUSION

Oxidative stress is in the foreground of cataract formation. Although aging itself can play a role in generating oxidative stress, but our results clearly indicate oxidative imbalance is more pronounced. It seems the increased production of SOD and GPx enzymes cannot compensate this imbalance. Further studies should be conducted to elucidate the molecular mechanisms by which antioxidants modulate their protective role, in order to identify potential pathways; and more importantly, new protective factor.

Although this research was carefully done, but, we are still aware of its limitations and shortcomings. First of all,

the research was conducted in senile cataract only. Second, the sample size was small.

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ORIGINAL ARTICLE

Comparison of Topical Versus Peribulbar Anesthesia for 23G Pars Plana Vitrectomy

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Abstract

Objective: To compare the safety and efficacy of topical anesthesia versus peribulbar anesthesia for 23-gauge pars plana vitrectomy.

Study Design: Randomized controlled trial.

Place and Duration of Study: Ophthalmology Department, Lahore General Hospital, Ameer-ud-Din Medical College, Postgraduate Medical Institute, Lahore from April 2013 to March 2016.

Methodology: A total of 110 patients were equally divided (n=55) in group A (topical anesthesia) and group B (peribulbar anesthesia). In group A, pledget soaked with 0.5% proparacaine hydrochloride were placed in the superior and inferior fornices three minutes before surgery, and removed just before surgery. For group B patients, 3 ml of 0.5% bupivacaine was used for peribulbar anesthesia three minutes before surgery. Surgical time was noted from the placement of pledget in fornix till the eye pad placed in group A, and from the time of peribulbar anesthesia in group B till the eye pad placed at the end of surgery. All data was recorded in Excel sheet and p-values were calculated using online OpenEpi.

Results: The mean age of the patient was 56.28 ±13.76 years. Male patients were 78 (70.9%) and female patients were 32 (29.1%). Mean duration of surgery was 30.32 ±7.07 minutes and mean pain score was 2.30 ±0.98. There was a significant difference with respect to mean duration of surgery in patients who were given topical anesthesia (32.52 ±6.92 minutes) versus those given peribulbar anesthesia (28.12 ±6.57 minutes, p<0.001). Mean pain score in topical anesthesia group (3.11 ±0.89) was significantly higher as compared to peribulbar anesthesia group (2.67 ±0.91, p=0.011).

Conclusion: Topical anesthesia is as effective as peribulbar anesthesia in terms of patient comfort and duration of surgery for 23-G pars plana vitrectomy in patients with vitreous hemorrhage.

Key Words: *Topical anesthesia. Peribulbar anesthesia. Vitrectomy. Duration. Pain. Vitreous hemorrhage.*

INTRODUCTION

Local anesthesia used for vitreoretinal surgery includes retrobulbar anesthesia,[1] peribulbar anesthesia,[2] subtenon anesthesia,[3] and even topical anesthesia.[4] Anesthetic injections are associated with many serious complications, although most are rare.[3]

In ocular surgery, topical anesthesia has many focal points over different types of local anesthesia involving needle injection. The benefits of topical anesthesia include early visual rehabilitation, easy approach, cheaper and less needle related trauma associated with local anesthesia.[5] In phacoemulsification cataract surgery, topical anesthesia is usually used worldwide and has proven effective for trabeculectomy,[4] selected cases of pterygium, strabismus, corneal trauma, and penetrating keratoplasty.[6,7]

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Conventional 20-guage, 23-guage, and 25-guage sutureless vitrectomy surgeries are being performed under topical anesthesia. Furthermore, their correlation with retrobulbar and peribulbar anesthesia have been reported.[8] Safety and effectiveness of topical anesthesia versus peribulbar anesthesia for 23-gauge vitrectomy without sedation was assessed by Mahajan *et al*. in patients with vitreous hemorrhage. Supplementation of anesthesia and sedation was not done in any of the patient. Maximum pain was noted in topical anesthesia patient during trocar entry; whereas in peribulber anesthesia, maximum pain was noted during block. Conjunctival chemosis and post-block lid edema was also noted in latter group patients.[9]

The rationale of this study was to determine which technique among topical anesthesia and peribulbar anesthesia for 23-g vitrectomy without sedation is better regarding patient's comfort, tested by visual analogue scale score and duration of surgery recorded in minutes from start of surgery to end of surgery. No such local study has been done in our population. The technique with less duration and greater patient's ease will be preferred in future.

The objective of this study was to compare the safety and efficacy of topical anesthesia versus peribulbar anesthesia for 23-gauge pars plana vitrectomy.

METHODOLOGY

The study was conducted at the Department of Ophthalmology, Lahore General Hospital, Ameer-ud-Din Medical College, Postgraduate Medical Institute, Lahore from April 2013 to March 2016. After the approval from Ethical Review board, informed consent was taken from all patients. Personal profile of each patient (including name, age, gender, patient registration number and address) was noted. Every patient underwent detailed preoperative work-up including best-corrected visual acuity (BCVA), and intraocular pressure (IOP) measurements, using applanation tonometer, was done. Anterior chamber and vitreous examination was done by slit lamp biomicroscopy. A total of 110 patients were equally divided in group A topical anesthesia (55 patients) and group B peribulbar anesthesia (55 patients). Pupillary dilatation was obtained with 1% tropicamide before surgery. In group A, pledget soaked with 0.5% proparacaine hydrochloride were placed in the superior and inferior fornix 3 minutes before surgery and removed before surgery. The eye as well as surrounding area was cleaned and painted with povidone iodine 5%. After draping, speculum was inserted and surgical procedure started. In group B patients, three ml of 0.5% bupivacaine was used for peribulbar anesthesia three minutes before surgery. Surgical time was noted from placement of pledget in fornix till the eye pad placed at the end of surgery in group A and from time of peribulbar anesthesia till the eye pad placed at the end of surgery in group B. Patients were well explained before the anesthesia that they will reply the visual analogue pain scale and mark the pain score on visual analogue pain scale, at the end of surgery, about the pain they felt from anesthesia to end of surgery; and if the severity of pain is beyond the bearing, the anesthesia may be augmented.

All of the surgeries were done by the same surgeon (HAK) in a standardised fashion (three-port double system pars plana entry and infusion cannula lower temporal area) using the associate surgical systems and 23-gauge surgical instruments (D.O.R.C. Dutch Ophthalmic Research Center; Zuidland, The Netherlands). At the end of surgery, the microcannulas were removed, and the sclerotomy sites were compressed with a cotton tip to allow self-sealing and adjust the conjunctiva to its original position. After surgery, patients were taken to the postoperative area, where vital signs were obtained and the observer collected patient pain assessment responses. Patients were shown a visual analogue pain scale (VAPS) with numeric ratings from 1 (no pain and discomfort) to 10 (severe pain and discomfort). Patients were asked to fill VAPS for the pain during surgery. If patients were unable to see the scale or read the accompanying text, the scale was described, and a score was obtained verbally. The surgeon also completed a questionnaire on the surgical conditions, complications, and need for supplemental anesthesia.

After the assessment of inclusion criteria, simple random sampling by envelope technique was applied. Patients of age between 50-70 years of both genders, with vitreous hemorrhage, were included in this study. Patients with nystagmus (examined clinically), claustrophobia, serious impairment of coagulation; shown by deranged PT/APTT 1) PT greater than 15 seconds 2) APTT greater than 50 seconds, patients who were unable to cooperate in maintaining a relatively motionless supine position and patients having language barrier and mentally handicapped were not included in this study. Sample size was calculated by using mean surgical time; it was 33.7 ±7.1 in group A and 30.1 ±6.2 in group B with 5% level of significance and 80% power of test.[10] Calculated sample size was 108, rounded off to 110.

Data was collected through a well-defined proforma and recorded in Excel sheet and p-values of statistical test were calculated by using online Statistical Software OpenEpi. Numeric data like age, anesthesia was presented as mean and SD; whereas, qualitative data like gender was presented in frequencies and percentages. Independent sample t-test was applied to compare both groups for pain and duration of surgery. P-value <0.05 was taken significant.

RESULTS

One hundred and ten cases were enrolled in this study after fulfilling inclusion criteria. The mean age of the patients was 56.28 ±13.76. Male cases were 78 (70.9%) and female cases were 32 (29.1%). Mean duration of surgery was 30.32 ±7.07 minutes, while patient's ease was 2.30 ±0.98. There was a significant difference with respect to mean duration of surgery in patients who were given topical anesthesia 28.12 ±6.57 minutes versus those given peribulbar anesthesia (32.52 ±6.92 minutes, p<0.001). Similarly, patient's pain score was significantly higher in topical anesthesia (3.11 ±0.89), which was comparable with peribulbar anesthesia (2.67 ±0.91, p=0.011, Table I).

Table I: Comparison of surgical procedure with parameters.

Parameters	Peribulbar anesthesia (n = 55)	Topical anesthesia (n = 55)	p-value
Duration of surgery	32.52 ±6.92	28.12 ±6.57	<0.001*
Ease score	2.67 ±0.91	3.11 ±0.89	0.011*

Continuous variables were presented as mean ± standard deviation and independent t-test was applied.
**P-value < 0.05 was considered as significant.*

DISCUSSION

Topical anesthesia regained prominence since it evacuated complications from regional anesthesia, expanding certainty and patient-safety, owing to improvements in monitored anesthesia care and short-acting anesthetic use.[11] There are different modalities of topical anesthesia including anesthetic drops, gels or sponges; those are applied to the conjunctival sac and

to prevent its loss via NLD gentle pressure as applied at lacrimal sac.[10] Commercially available local anesthetics include amethocaine, lignocaine, and bupivacaine. Instillation of local anesthetic decreases intraocular pressure (IOP).[12]

Being of very brief duration, it requires repeat instillation of drops after every 0.5 hours. Long-term use is associated with toxic potential. Topical anesthesia is increasingly used nowadays, and close cooperation with the patients during the operation is required.[13]

The peribulbar technique is another widely employed block that has been introduced in ocular anesthetic practice more recently.[14] This procedure involves the injection of local anesthetic mixture externally to the muscle cone. Consequently, it may be called 'extraconal' block. The needle entry point is the same as that of retrobulbar block, which is from two-thirds lateral to the inferior rim of the lower conjunctiva. The needle may be advanced from the lower lid with a skin wheal or through the conjunctiva after topical anesthetic drops have been applied.[15]

The needle is introduced directly and is shorter than the former technique. It is advised to use 26G 25 mm needle and a modified technique is the use of 23G needle that has resulted in improvement in the outcome.[16] In selected cases only, 23-gauge sutureless vitrectomy under topical anesthesia is safe and effective.[17] The expansion of day-case facilities has encouraged its use, and the development of less invasive surgical technique has rendered general anesthesia largely unnecessary. Retrobulbar and peribulbar blocks are commonly practiced in ocular procedures among local anesthesia.[18] While providing excellent conditions for operating the eye, these techniques are associated with serious but uncommon side-effects. The most dangerous side-effect is respiratory arrest as a result of brainstem anesthesia, others include ptosis, conjunctival chemosis, increased IOP, cranial nerve palsies, diplopia, retinal vascular occlusion and optic nerve damage.[19] Lid edema and bruising due to peribulbar block is also cosmetically unacceptable in certain postoperative cases.[20] In this study, no such complications were noted in patients having peribulbar anesthesia. Less invasive techniques for providing local anesthesia, such as subconjunctival or topical application of local anesthetic, are devoid of such risks, but fail to provide adequate akinesia of the eye and postoperative analgesia. As 23G pars plana vitrectomy technique was used, so no conjunctival incision or cautery was administered. In this study, group A patients experienced pain during trocar insertion and removal of cannula, while group B patients experienced pain during peribulbar injection and endolaser; same trend was demonstrated by Hande Celiker *et al*.[21] In both groups, supplemental IV medications were not administered showing the efficacy of topical and peribulbar anesthesia, which is comparable for pars plana vitrectomy.

Scared conjunctiva, as a result of previous retinal procedures, was not taken for the study as it may have quite difficult manipulation which may result in bias. Topical anesthesia with intravenous midazolam and fentanyl citrate were also used by Yepez *et al*. for scleral buckling; but the authors did not include patients for scleral buckling as it is a painful procedure, if done in local anesthesia.[22]

Adequate akinesia of extraocular muscles is very critical in retinal surgery which is not achieved by topical anesthesia, so manipulation of intraocular structures under topical anesthesia is tricky. Unwanted extraocular motility may result in many iatrogenic complications such as iatrogenic holes and breaks, pre-retinal hemorrhage or retinal incarceration. Intraocular instruments passing through the pars plana may help overcome the unsteadiness of eye during surgery. In this study, no iatrogenic complication, due to movement of the eyeball, was noted which was compatible with previous studies.[23]

Topical anesthesia obviously eliminates the risk of globe perforation, retrobulbar hemorrhage, damage to the optic nerve, and significant conjunctival chemosis. The topical anesthesia technique appears to provide acceptable analgesia during surgery, wears off rapidly after surgery, and does not interfere with the patient's ability to blink, see, or move the eye.[24] In the present study, these observations were confirmed. Patients were able to follow commands, and movement of the eyeball was controlled by the surgeon through the surgery with the use of intraocular instruments.

A study was done for topical and peribulbar block in cataract surgery on 115 patients, and reported that surgical procedure time was significantly high in peribulbar group. There was no difference between topical and peribulbar groups for pain intensity and satisfaction of patient.[24] While in another study, mean overall patient's pain score was 1.77 ±0.50 in topical and 1.77 ±0.43 in peribulbar anesthesia. Patient's comfort score was recorded as 0.3 ±0.53 and 0.17 ±0.38 in topical and peribulbar anesthesia, respectively; while mean surgical time was 33.7 ±7.1 minutes and 30.1 ±6.2 minutes in topical and peribulbar anesthesia, respectively. These mean values were not statistically significant ($p>0.05$).[23] In this study, the results were different as the mean surgery time was 28.12 ±6.57 with topical 32.52 ±6.92 with peribulbar anesthesia and the p-value ($p<0.001$) was significant; while the mean patient's pain score calculated by visual analogue pain scale was 2.67 ±0.91 with peribulbar and 3.11 ±0.89 with topical anesthesia, respectively; and these means were also statistically significant ($p=0.012$). The results showed that both peribulbar and topical anesthesia are

equally effective for pars plana vitrectomy, and avoid the risks and consequences of general anesthesia.

CONCLUSION

Topical anesthesia is as effective as peribulbar anesthesia in terms of patient's comfort and duration of surgery for 23-G pars plana vitrectomy in patients with vitreous hemorrhage.

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ORIGINAL ARTICLE

Relation between Depressive Disorder and Iron Deficiency Anemia among Adults Reporting to a Secondary Healthcare Facility: A Hospital-Based Case Control Study

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Abstract

Objective: To determine the relationship between iron deficiency anemia and depressive disorder; and identify the correlation between severity of anemia and depressive disorder.

Study Design: Descriptive, analytical study.

Place and Duration of Study: Department of Psychiatry and Medical Reception Center, Sindh Rangers Hospital, Karachi (a secondary healthcare facility), from January to July 2017.

Methodology: Depressive disorder was diagnosed by psychiatrist on ICD 10 criteria and severity of symptoms was assessed on HAM-D rating scale. Hundred cases and equal number of age and gender matched controls were enrolled in the study. A semi-structured proforma was used for documenting the socio-demographic factors and outcome variables. Blood samples were taken for Hemoglobin (Hb) level and peripheral film from both groups.

Results: Median Hb levels were 11.9 (IQR=1.27)) for depressed patients versus 12.9 (IQR=1.3) for healthy participants. Significant difference between Hb levels of two groups was found ($p<0.001$), i.e. depressed participants were found to have higher frequency of anemia (73%) as compared to non depressed participants (16%, $p=0.001$). Spearman rank correlation coefficient for Hb level and depression was -0.429 ($p<0.01$), showing significant negative correlation. The odds for Hb level were 0.487 (0.37-0.64), which showed that cases are less likely to be found with higher Hb levels as compared to controls ($p<0.001$).

Conclusion: This study concludes that there is relationship between iron deficiency anemia and depressive disorder; and severity of symptoms of DD increases with degree of IDA.

Key Words: *Adults. Depressive disorder. Iron deficiency anemia.*

INTRODUCTION

Depressive Disorder (DD) is one of the most common mental disorders worldwide. Approximately 300 million people are affected by DD globally.[1] Etiology of depressive disorder is broadly classified into two major categories, i.e. non-modifiable (genetic) and modifiable (environmental).[2] Nutrition is an important modifiable etiological factor. Many nutrient deficiencies (such as folic acid, vitamin B12) have been linked to causation as well as severity of DD, thus correction of these deficiencies can play significant role in prevention as well as treatment of DD.[3] No such specific causative relation has yet been established between iron deficiency and DD. However, there are some facts that force us to consider this factor. The clinical presentation of patients, affected by iron deficiency anemia (IDA), often mimics that of depressive disorder, such as lethargy, irritability and behavioural disturbances. Of note, many of these signs and symptoms precede the establishment of frank anemia.[4] Iron supplementation leads to improvement in depressive symptoms even before any visible improvement in RBC count is observed. It seems that this phenomenon is due to the recovery of neurotransmitters and enzyme levels, dependent on iron, unrelated to hemoglobin (Hb) concentration.[5] With the identification of the use of iron supplements in treatment of isolated depressive symptoms of IDA, extended knowledge is needed to identify any relationship of iron deficiency with DD, and the usefulness of iron supplements in its treatment, in particular.

If the association of IDA with DD is established, it can prove to be a breakthrough in effective management of the latter. Moreover, mental health professionals can be sensitised to the need of assessing the Hb status of patients of . Thus, the concept of holistic medicine will be satisfied,[6] which states that all the biological, psychological as well as social aspects of the patients must be considered during treatment. This cost-effective and easy treatment is not studied in Pakistan earlier.

The objective of this study was to determine the relationship between iron deficiency anemia and depressive

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disorder; and identify the correlation between severity of anemia and depressive disorder.

METHODOLOGY

It was a hospital-based case control study, conducted at Sindh Rangers Hospital, Karachi, from January to July 2017. Cases and equal number of age and gender matched controls were enrolled by purposive sampling technique. Patients presenting to psychiatry OPD, aged between 18-60 years, were assessed. Cases were selected on uniformly accepted criteria as diagnosed patients of depressive disorder by consultant psychiatrist on ICD10 criteria,[7] with score of 8 and above on HAM-D rating scale (a standardised tool for indication and assessing severity of depressive disorder).[8]

Other psychiatric disorders were carefully excluded such as, schizophrenia, post-schizophrenic depression, bipolar affective disorder, and substance use disorders by psychiatrist. Chronic medical disorders (such as chronic liver disease, chronic renal disorders, hypothyroidism, and hyperthyroidism) were also excluded. Moreover, women who were pregnant or were in postpartum period were also excluded.

Age and gender matched controls, fulfilling the inclusion and exclusion criteria, were selected from other OPDs of the same hospital and from the attendants coming with the patients, as well. A semi-structured proforma was used for documenting the socio-demographic factors and outcome variables, i.e. score on HAM-D and hemoglobin (Hb) levels. The severity grouping were done on the basis of scores; participants having score 0-7 were labelled as without depression, 8-17 as mild depression, 18-24 moderate depression, and score more than 24 as severe depression.

Hemoglobin levels (Hb) were assessed in all the cases and controls. WHO criteria were used for the diagnosis of anemia.[9] In females, Hb $\geq$12 g/dL was considered as normal, 11 to 11.9 g/dL as mild anemia, 8 to 10.9 g/dL as moderate anemia, and <8 g/dL was considered as severe anemia. In males, $\geq$13 g/dL was taken as normal, 11 to 12.9 g/dL as mild anemia, 8 to 10.9 g/dL as moderate anemia, and <8 g/dL as severe anemia. Low Hb along with mean corpuscular volume (MCV) less than 80 fL, and microcytic picture on slide was taken as diagnostic standard for IDA. Other causes of microcytic anemia, i.e. sideroblastic anemia, thalassemia, and lead poisoning were ruled out on peripheral smear.

Sample size was estimated using Openepi sample size calculator version 3.01. Inserting mean and standard deviation of HAM-D scores of participants with anemia and without anemia; 32.09 ±4.19, 33.37 ±1.9 at 95% CI,[10] the sample size was found to be 204, i.e. 102 cases and 102 controls. From the initial sample of 204 participants, the patients with missing data of Hb and an equal number of controls were excluded making a final sample size of 200.

Ethical clearance was taken from institutional review board. Informed consent was obtained from the participants after informing them in simple and understandable language about the purpose of study. They were assured of confidentiality and allowed to withdraw at any point of study without mentioning the reason.

The data collected was analysed using computer packages, Statistical Packages of Social Sciences (SPSS version 22). Normality of Hb and HAM-D scores was assessed using Shapiro Wilk test, mean and standard deviation (SD) were computed for quantitative variable, e.g. age. Categorical variables were measured in frequencies and percentages. Stratification was done with regard to gender, age group, and socioeconomic status, for the outcome variables, (i.e. depressive disorder and anemia), in order to see the impact of these on the outcome variables by using Pearson Chi-square test of independence; p-value less than 0.05 were considered as significant. Mann-Whiteny U-test was used to compare median Hb levels between the two groups and median with interquartile range (IQR) was reported. Spearman rank correlation analysis was employed to examine the relationship between depression and Hb levels. In order to determine the degree of relationship between depression and Hb levels, logistic regression analysis was used, and odds ratio with p-value less than 0.05 were considered significant.

Table I: Characteristics of the patients with IDA and control subjects.

Characteristics	Control (n=100)	Cases (n=100)	P-value
Age			
18-25 years (n=34)	18	16	0.99
26-35 years (n=41)	21	20	
36-45 years (n=68)	33	35	
46-55 years (n=53)	26	27	
>55 years (n=4)	2	2	
Gender			
Female (n=130)	64	66	0.76
Male (n=70)	36	34	
Marital status			
Single (n=36)	23	13	0.125
Married (n=155)	75	80	
Widowed (n=5)	1	4	
Separated (n=4)	1	3	
Socioeconomic status (monthly income)			
Lower (Rs <14000 per month) (n=74)	39	35	0.81
Middle (Rs =14000-45000) (n=102)	50	52	
Upper (Rs > 45000) (n=24)	11	13	
Residence			
Rural (n=80)	40	40	1
Urban (n=120)	60	60	
Anemia			
Normal (n=111)	84	27	<0.001
Mild (n=82)	16	66	
Moderate (n=6)	0	6	
Severe (n=1)	0	1	

Table II: Association between anemia and score at HAM-D.

Anemia	Score at HAM-D								p-value
	Normal		Mild depression		Moderate depression		Severe depression		
	n	%	n	%	n	%	n	%	
Normal	84	84.0	14	26.4	8	29.6	5	25.0	<0.01*
Mild	16	16.0	36	67.9	18	66.7	12	60.0	
Moderate	-	-	2	3.8	1	3.7	3	15.0	
Severe	-	-	1	1.9	-	-	-	-	

**p<0.05 was considered significant using Pearson Chi-suare test of independence.*

RESULTS

Mean age of the 200 participants entering this study was 37.74 ±10 years with mean age of cases and controls as 38.19 ±10.2 years and 37.28 ±9.97 years, respectively; 65% (n=130) of the participants were female. Fifty percent (100) of the study participants were depressed with median HAM-D score 18 (IQR=10). Distribution of Hb and HAM-D scores was not normally distributed, the Shapiro Wilk test gives p-value less than 0.05 for both variables. Therefore, we used non-parametric test to compare the median of two groups. Other characteristics of the study population are described in Table I.

Median Hb levels were 11.9 g/dl (IQR=1.27) and 12.9 g/dl (IQR=1.3)) in depressed and healthy participants, respectively. The median differences of Hb between two groups were found statistically significant with p <0.01 (Figure 1). In depressed individuals, median HAM-D was 18 (IQR=10); and in healthy individuals the median HAM-D was 5 (IQR=3). Mann-Whitney U-test showed that median HAM-D scores of the two groups were significantly different (p<0.01).

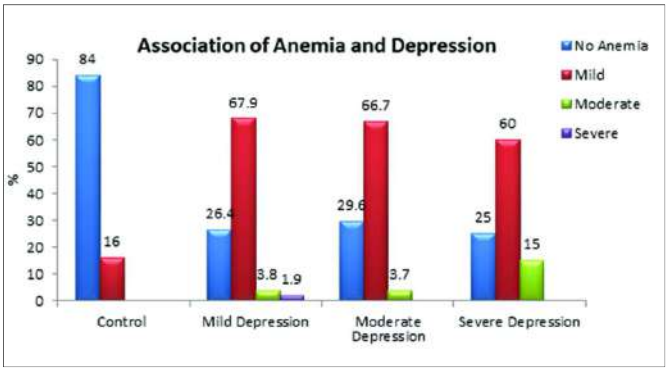

Figure 1: Relationship of anemia with depression (p <0.01) obtained using Pearson Chi-square test of independence.

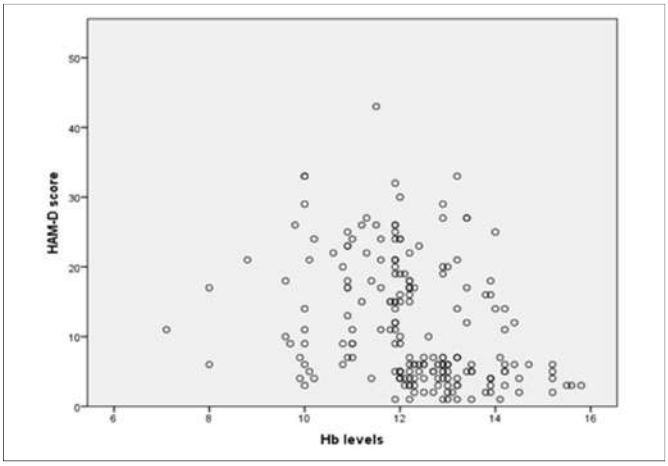

Figure 2: Spearman rank correlation between Hb concentration and HAMD rating scale in 200 adults (r = -0.429, p <0.01).

There was a significant association obtained between HAM-D scores and anemia, using Pearson Chi-square test with p-value less than 0.01. In this study, 67.9% cases of mild anemia were found with mild depression; and 3.7% cases of moderate anemia were found with moderate depression (Table II).

Spearman rank correlation coefficient for Hb level and depression was r = -0.429, and statistically significant (p<0.01) which showed negative relation (Figure 2).

The odds for Hb levels 0.487 (0.37 - 0.64) showed cases are less likely to be found with higher Hb levels as compared to controls, p-value was less than 0.05.

DISCUSSION

This study evaluated the relation between Hb levels and DD. Median Hb levels were 11.9 g/dl (IQR=1.27) and 12.9 g/dl (IQR=1.3) in depressed and healthy participants, respectively (p=0.01). IDA was observed in 44.5% of the participants, which seems higher than global estimates.[11] It might be due to the reason that 88% of our study population belongs to middle and low socioeconomic class in which IDA is more common, results similar to previous studies.[12,13] Higher frequency of IDA in depressed participants as compared to controls may indicate the role of iron in brain function and the development of DD. The scores at HAM-D raised significantly with decreasing Hb levels. These findings are similar to a study conducted in Iran.[10] In this study, although the correlation coefficient was low; but direction showed an inverse correlation between Hb level and severity of depression. These results are consistent with those of the study conducted in Iran on medical students showing that Spearman correlation coefficient for ferritin and depression was -0.167 and statistically significant.[14] Similar results were observed in a study on Japanese male population.[15]

The current study evaluated that IDA was associated with a significantly increased risk of DD, odds for Hb level 0.487 (0.37-0.64). These results supported by a

study conducted in Italy, showing strong association of anemia with depression in elderly population with odds ratio [OR] = 1.93; 95% confidence interval [CI], 1.19-3.13).[16] However, Yi *et al*. and Millingen *et al*. concluded that there was no association between IDA and depression.[15,17] This discrepancy may be due to sample differences, ethnic differences or different depression rating.

Future researchers could determine whether intervention with iron supplementation can relieve symptoms of depression in clinical trials. Future studies should also assess the multidimensional syndrome of depression by using an array of converging measures.

This study was limited by a small sample size and a hospital-based environment. The results need to be replicated ideally with large sample size. Moreover, to establish causal association between IDA and DD, role of iron supplements in patients with DD should be studied in clinical trials.

CONCLUSION

This study concludes that there is relationship between iron deficiency anemia and depressive disorder; and severity of symptoms of DD increases with degree of IDA. However, it needs validation with larger sample size and trials.

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REVIEW ARTICLE

Managing Hot Flushes in Menopausal Women: A Review

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ABSTRACT

Hot flushes during menopause are distressing for women and result in poor quality of life. Purpose of the current review was to evaluate the available treatment modalities that should be utilised for the management of hot flushes. Menopause refers to last menses of women life and can be declared after amenorrhea of 12 months. Vasomotor symptoms including hot flushes and night sweats are common after menopause, affecting almost 50 - 85% women older than 45 years. The mean increment in core body and skin temperature is 0.5°C and 0.25 - 3°C during a hot flush attack. Low level of estrogen during menopause and its association in triggering episodes of hot flushes, is still under debate. The most accepted hypothesis is a narrowing of the thermoneutral zone (TNZ) triggered by estrogen fluctuations. Although, hormone replacement therapy (HRT) remains the standard treatment for the alleviation of such symptoms, incidence of life threatening side effects restrained medical professionals from its use. Complications associated with the use of HRT can be avoided by appropriate evaluation of patients before initiating therapy. Several guidelines have also recommended HRT (estrogen and progesterone) to be safe for up to a period of seven years. Both hormonal and non-hormonal treatments are used for the management of hot flushes. Since hot flushes are the least appreciated and neglected complication of menopause, current review provides detailed information on its background, pathophysiology and management, and emphasises the need of its treatment.

Key Words: *Menopause. Hot flushes. Hormone replacement therapy. Vasomotor symptoms. Climacteric symptoms.*

INTRODUCTION

Menopause (*menos*: month, and *pausis*: cessation), a critical phase in women life, is defined as last menses and can be declared after 12 months of amenorrhea. The average age of menopause is 51 years, but symptoms usually occur 10 years prior to this age (peri-menopausal symptoms). The hallmark of menopause is vasomotor symptoms including hot flushes and night sweating.[1] Hot flushes are characterised by sudden onset of heat sensation that begins in chest and may progress to the whole chest and the neck.[2] In addition to the vasomotor symptoms, menopause is also characterised by dynamic changes in endocrinology of female's body such as cycle irregularities, reduced fertility, and psychological symptoms. Menopause can also be induced artificially by surgical procedures (hysterectomy or oophorectomy), either by chemotherapy or radiations.[3]

About 50-70% women of menopausal experience several episodes of hot flushes and night sweats. These symptoms are more severe in women with surgical menopause as compared to natural menopause. Hot flushes, the most common and troublesome problem associated with menopause, are associated with a sharp rise in circulating luteinising hormone and epinephrine (a potent stimulator of heart function that increases heart rate, cardiac output, and systolic blood pressure) with a simultaneous decline in the hormone norepinephrine (which increases blood pressure dramatically).[4]

Flushes vary in intensity, frequency, and duration from one person to another. SWAN (Study of Women`s Health Across the Nation, having data of 16000 women) demonstrated that many women experience hot flushes on daily basis, some as frequently as every hour while some have weekly or monthly episodes. Majority of the women experience hot flushes for 6 months to 2 years where symptoms are severe after 2 years of menopause. These symptoms include discomfort, embarrassment, restlessness and loss of sleep. Sometimes an aura precedes hot flush by several seconds. During this period, heart rate and blood flow towards finger increase followed by a sensation that the flush is about to occur. Immediately, there will be an increase in finger temperature (up to 6°C), while a simultaneous decrease in body temperature (0.1 to

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0.6°C) would be experience as a result of sweating on forehead and chest.[5]

Epidemiology: Prevalence of hot flushes largely depends upon the culture and ethnicity. Table I shows varying incidence of hot flushes among different ethnic groups. According to an estimate, 50-85% women older than 45 years embraced hot flushes during their life.[6] United State census bureau statistics shows the incidence of hot flushes as 75% among women older than 50 years.[5]

The Prevalence of hot flushes in different ethnic groups is 46% in African Americans, 34% in Hispanics, 31% in Whites, 21% in Chinese, and 18% in Japanese.

Evaluation of Vasomotor Symptoms: Women presenting with classic hot flushes between the ages of 40 - 50 year do not require laboratory examination. However, other causes of hot flushes, if suspected, must be ruled out. These causes include alcohol consumption, carcinoid, the dumping syndrome, hyperthyroidism, narcotic withdrawal, pheochromocytoma, and medications including nitrates, niacin, gonadotropin-releasing hormone agonists, and anti-estrogens. Usually, the levels of FSH and LH fall in normal range in menopausal transition.[7] Temperature changes can be assessed with thermography as temperatures of finger and toes increase about 20 to 33°C during hot flushes.[8] The increment in core body temperature and mean skin temperature is 0.05°C and 0.25-0.3°C, respectively during hot flushes.[9]

Pathophysiology of hot flushes: The underlying mechanism of hot flushes is debatable to date. Studies on animals (monkeys and rats) with surgically induced menopause suggest that decline in estrogen levels as a result of menopause is the main cause of hot flushes.[10] Contrary to this, low and high levels of estrogen are observed among pre-pubertal and pregnant women, respectively; but low level of estrogen during pre-puberty does not lead to hot flushes among young girls. Pregnant women may incur hot flushes despite high levels of estrogen. Although hot flushes are first symptom of menopause transition; but they subside after menopause, when estrogen levels are markedly low. Despite these contrary findings, most of the investigators believe a relationship between estrogen levels and hot flushes.[8]

Many investigators have proposed different hypothesis to explain underlying mechanism of flushes; but recently, Robert Freedman presented an attractive explanation based on thermoregulation. Thermoregulation in human body is controlled by hypothalamus *via* neurotransmitters (serotonin, nor-epinephrine) and neuromodulators (estrogen). There is a thermo-neutral zone of about 0.4°C in normal and asymptomatic women. Within this zone, fluctuations in core body temperature do not result in initiation of compensatory mechanisms including

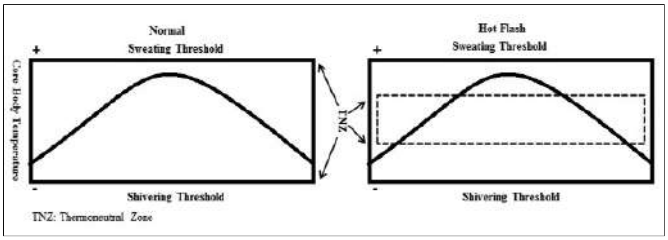

Figure 1: Thermoneutral zone in asymptomatic (normal) and symptomatic (hot flush) women.

flushing and sweating. On the other hand, in symptomatic women, thermo-neutral zone becomes narrow as a result of increased central noradrenergic activation caused by changes in estrogen level as shown in Figure 1.[11] Due to narrow thermo-neutral zone, fluctuations in core body temperature causes hot flushes and sweat.[12]

The relationship between estrogen and hot flushes can also be explained with Hemmie`s hypothesis, which states that estrogen enhances synthesis of 5HT and endorphins, which in turn, inhibit the production of noradrenaline. As menopause results in deficiency of estrogen, it results in decrease level of 5HT and endorphins, followed by an increase in noradrenaline level. This increase in noradrenaline causes narrowing of thermal neutral zone and results hot flushes.[13] Other theories, explaining pathophysiology of hot flushes, state the altered sensitivity of cutaneous vessels and changes in level of circulating gonadotropic hormones might contribute to exaggerated response, i.e. hot flushes.[14,15]

Treatment options: As far as treatment of menopause and its associated symptoms are concerned, there are two schools of thought, one in favour of treatment considering the fact that menopause is a result of hormone deficit and should be treated; while other not in favor of treatment considering menopause as a natural process that subsides with the passage of time.[16] Women having hot flushes due to menopause face significantly lower quality of life that is inexplicably associated with loss of productivity. Such women bear disruption in family relationship, social isolation, anxiety, embarrassment, fatigue, osteoporosis, bone fragility and sleep disturbance.[17,18] These symptoms should be addressed to improve the quality of life during peri- and post-menopausal phase.[6,19] There are several approaches to manage vasomotor symptoms during peri-menopausal and post-menopausal women. Depending on the severity of symptoms (mild, moderate, severe) treatment approach is selected as shown in Figure 2.

Hormonal Treatments (HT): It includes treatment with estrogen alone (in case of hysterectomy) or in combination with progesterone (in case of intact uterus) to protect from endometrial hyperplasia.[21] International Menopause Society and America Association of Endocrinologists guidelines recommend HRT therapy as most effective treatment for vasomotor symptoms and

Table I: Hormone replace therapy (HRT) side effects and contraindications.[27,28]

Agents	Side Effects	Contraindication
Estrogen	Breast tenderness, nausea, headache, bloating; may resolve by continuous use, decrease dose or substitution with other agents	Unexplained vaginal bleeding, acute liver disease, acute thromboembolic disease, known or suspected breast cancer, caution should also be taken in cardio vascular disease and hypertriglyceridemia
Progesterone	Alteration in mood, breast tenderness, bloating; can be alleviated by switching to another progestogenic agent.	Known or suspected breast cancer, pregnancy and undiagnosed vaginal bleeding.

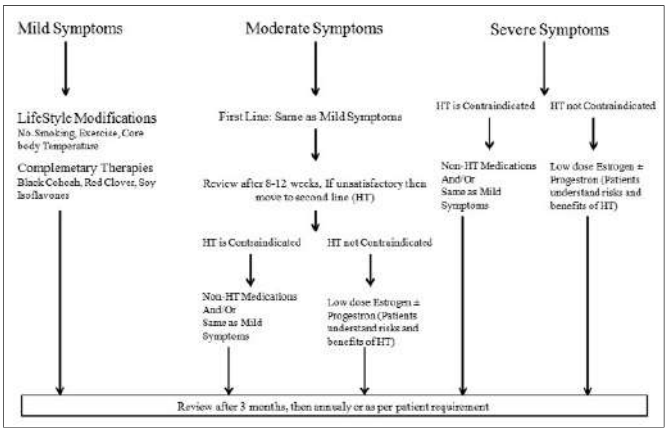

Figure 2: Severity-based management strategies for patients having hot flushes.[20]

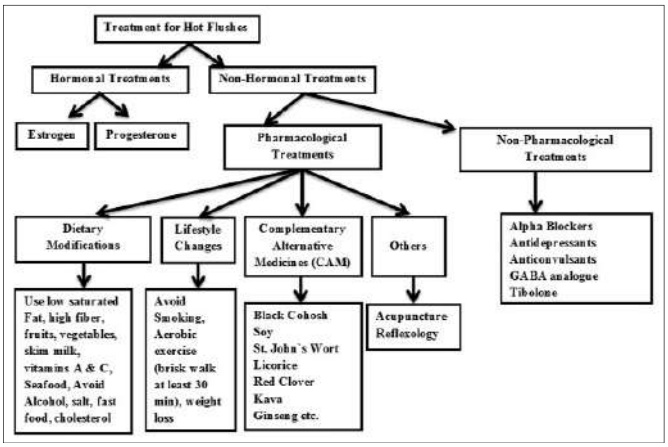

Figure 3: Treatment summary for hot flushes.[22,30,33]

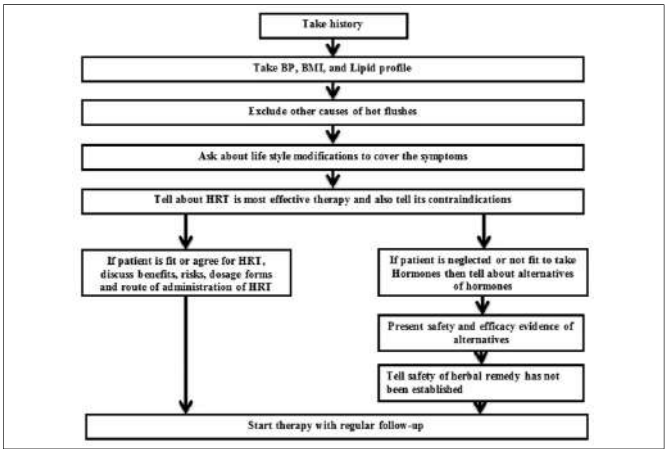

Figure 4: Clinical approach to manage hot flushes.

for maintaining the improved quality of life.[21,22] On the contrary, studies have shown that HRT may cause coronary heart disease, strokes, venous thrombo-embolism and invasive breast cancer.[23] These findings left both the healthcare professionals and the patients ambiguous regarding HRT use.

Recent recommendations from International Menopausal Society on the use of HRT state that estrogen-progesterone combination or estrogen alone can be safely used for five and seven years respectively, in first time users. Review of 45 studies (1975-2000) showed that there is no significant risk of breast cancer with HRT and short duration therapy does not elevate the risk of breast cancer.[22] Besides all these controversies and recommendations, lifestyle modifications and OTC remedies should be approached for mild symptoms before considering HRT.[20]

Before initiation of HRT, evaluation of patient`s medical history should be done carefully to check for family history of breast, ovary and endometrium carcinoma, deep venous thrombosis, gall stone, migraine and epilepsy. Screening for blood sugar and lipid profile tests should be mandatory during HRT.[24]

HRT is effective for the prevention of hot flushes as well as fracture associated with menopausal osteoporosis. It may be cardio protective if started at the time of menopause.[25] HRT can also be used in breast cancer survivors and debate is still present, as some data show increase in recurrence of breast cancer with HRT, while few studies contravene it. Complementary therapies are still less effective as compared to HRT.[26] The benefits, side effects and contraindications are described in Table I.[27,28]

Non-hormonal treatment: Undoubtedly, hormonal treatment has potential benefits, but it is also associated with risks including breast cancer and endometrial hyperplasia.[27,28] Such risks have shifted attention of healthcare professionals towards non-pharmacological treatment options, resulting in wide use of them. According to a survey, 76% women use alternative therapies for the management of symptoms associated with menopause.[29] A brief overview of these interventions is shown in Table II. Non-hormonal pharmacological therapy includes alpha adrenoceptors agonist (methyldopa, colinidine and lofexidine), antidepressants and anticonvulsants, GABA analogue (Gabapentin).[30]

Tibolone is an alternative of HRT being used in current practice. It is a synthetic steroid developed for the treatment of climacteric complaints. Tibolone has estrogenic, progestogenic and androgenic effects. Its effects are comparable with estrogen-based HRT.[31] It is metabolised in liver to its metabolites, which bind on estrogen, progesterone and androgens receptors. However, Tibolone has a tendency to induce greater vaginal bleeding as compared to conventional HRT and is associated with increase relative risk of breast cancer and endometrial hyperplasia.[32-34]

Table II: Non-pharmacological treatment of hot flushes.[24]

Lifestyle modification	Measures
Lifestyle measures advices	Avoid smoking
	Aerobic exercise
	Weight loss measures
Dietary modifications advices	Use diet having low saturated fat and high fiber
	Use fruits and vegetables
	Use seafood and skinless chicken
	Use skimmed milk and its products
	Avoid high cholesterol and fast food
	More than 5 servings of fruits and vegetables per day
	Diet having antioxidant vitamins would be preferred over vitamin supplements
	Use salt up to 6 g/day
	Supplements of vitamin A and C (vitamin E: 800 iu/day)

Complementary alternative medicines (CAM): Various herbs and food supplements have made their place for the alleviation of vasomotor symptoms in menopausal women. Phytoestrogens are structurally related to estrogen (estradiol) and are present in several plant species including red clover, flax seed and soy.[35] Soy isoflavones have estrogenic properties and are mostly used by Asian women for the treatment of hot flushes. A comparative study among Western and Chinese women shows the incidence of hot flushes of 80% and 20%, respectively. This difference between incidences is attributed to dietary soy intake among Chinese population.[36,37] Table III summarises commonly used botanical products for the management of menopausal symptoms.[38]

Traditional acupuncture is beneficial for the treatment of vasomotor symptoms in breast cancer patients in conjunction with HRT.[39,40] Reflexology is also used for the treatment of menopausal symptoms and referred to

Table III: Complementary and alternative medicines for the treatment of menopausal symptoms.[35,38]

Herb	Proposed mechanism	Usual dose	Side effects
Black Cohosh *(Cimifuga Racemosa)*	Estrogenic and progestogenic effects	20 mg twice daily	GIT complaints, hypotension, dizziness, nausea, allergic reactions
Soy	Estrogenic effects	40-60 gm soy protein powder or 50-80 mg isoflavones daily	Soy foods are well tolerated, soy powder can cause GIT complaints
St. John`s Wort *(Hypericum Perforatum)*	Inhibit reuptake of serotonin, nor-epinephrin, dopamin	No widely accepted dose	GIT complaints, allergic reactions, neuropathy, anxiety, fatigue
Red Clover *(Trifolium Pratense)*	Estrogen like effects	40-80-160 mg isoflavones per day	Breast tenderness, menstrual changes, weight gain
Kava *(Piper Mythysticum)*	Anxiolytic	No widely accepted dose	Stomach complaints, restlessness, allergic reactions, mydriasis
Dong Quai *(Angelica Sinensis)*	Estrogenic effects	No widely accepted dose	Bleeding, photosensitivity
Burdock *(Arctium Lappa)*	Estrogenic effect	Not available	Data not available
Licorice *(Glycyrriza Glabra)*	Estrogenic effects	Not available	Data not available
Motherwort *(Leonorus Cardiaca)*	Stimulate uterine activity	Not available	Data not available
Wild Yam *(Dioscorea Barbasco)*	Mode of action is undetermined	No widely accepted dose	No adverse effects
Evening Primose Oil *(Oenothera Biennis)*	Part of pathway of prostaglandins E1 synthesis	2-4 gm daily	Headache, GIT complaints
Ginseng *(Panax Ginseng)*	Estrogenic effects	Not available	Insomnia, diarrhea, vaginal bleeding, can cause Steven Johnson syndromes
Chasteberry	Unknown	30-40 mg per day	Data is not available
Flaxseed *(Linum Ussitatissimum)*	Estrogenic, antiestrogenic and steroid-like actions	25-40 gm per day	No known side effects
Geranium *(Pelargonium graveolens)*	Unknown	Not available	Data not available
Sage *(Salvia officinalis)*	Anti-hydrotic properties	Not available	Data not available

Table III: Complementary and alternative medicines for the treatment of menopausal symptoms.[35,38]

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applying pressure at specific points or areas of the feet. Though therapeutic benefits of acupuncture are established in the literature, but further clinical trials are needed to establish its potential role in the management of menopausal symptoms.[41]

Although, several reports have demonstrated the valuable effects of CAM in menopause, but data indicating the superiority of bio-identical hormones upon conventional hormone therapies are currently lacking. Moreover, the risk profile of CAM has not investigated in the available literature.[41] Treatment summary of climacteric symptoms is shown in Figure 3.[22,30,33]

Clinical approach to manage hot flushes: Clinical approach and management of hot flushes should be subjected to patient`s clinical condition, as described in Figure 4.[42]

CONCLUSION

Climacteric symptoms significantly affect the quality of life during menopausal age. Numerous studies have addressed the need of management of menopausal symptoms among both pre- and post-menopausal women. The selection of treatment modalities should be based on patient`s history and severity of symptoms. Moreover, education programmes on menopausal symptoms should be carried out at community level in order to increase awareness among general population and healthcare professionals. The authors are conducting a nationwide survey to evaluate the knowledge and awareness of menopause among general public and healthcare professionals in Pakistan. Preliminary findings of this project indicated a low awareness of menopause and its treatment among women in Pakistan.[43]

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CLINICAL PRACTICE ARTICLE

Clinical Outcome of Laminoplasty in Cervical Myelopathy

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ABSTRACT

Objective: The objective of the study was to assess the effectiveness of laminoplasty in terms of improvement in the Japanese Orthopedics Association (JOA) score in cervical spondylotic myelopathy (CSM).

Study Design: Descriptive study.

Place and Duration of Study: Department of Neurosurgery, Lahore General Hospital, Lahore, from June 2014 to October 2016.

Methodology: All patients having CSM were assessed preoperatively and postoperatively by JOA score and radiological findings. Preoperative X-rays of cervical spine were done to rule out kyphotic deformity. CT scan and MRI of cervical spine were obtained preoperatively to assess the pathology. Single-door laminoplasty with modified trauma plates were applied in each case by making the hinge over the right side. Digital cervical spine X-rays and CT scans with axial reconstruction were obtained postoperatively in all patients, ensuring spinal canal widening and stability.

Results: Among the 36 patients, 24 were males and 12 females, age ranging from 35 to 80 years. All the patients did extremely well with marked improvement in the symptomatology. The JOA scored improved in 32 patients, remained static in three patients and one patient had slight deterioration, which later on improved. Three patients developed postoperative kyphotic deformity, which settled in three months. Postoperative radiology showed significant increase in the axial diameter of spine.

Conclusion: Cervical laminoplasty remains an effective method for posterior decompression of spine. The most promising approach to cervical myelopathy ought to take into account both the features of patients and disease, as well as the competency and skills of the surgeon.

Key Words: *Cervical myelopathy. Spondylotic. Laminoplasty. Kyphotic deformity. Physiotherapy.*

INTRODUCTION

Cervical spondylotic myelopathy (CSM) is a degenerative condition causing osteophytes and spinal canal narrowing, resulting in cervical stenosis that often progresses to myelopathy presenting as motor or sensory deficit.[1] CSM develops secondary to stenosis or ossification of posterior longitudinal ligament. It is more frequent in elderly and middle-aged persons of either gender.[2] Conservatively, soft collars, NSAIDs, epidural steroid and physiotherapy are used as treatment modality.[3] Surgically, anterior or posterior approach is performed. Anterior approach allows decompression in kyphotic deformity.[4] Posterior approach compromises of laminoplasty or laminectomy. The outcomes of laminectomy are poor in the young; but it is a good option in elderly patients with ossification of the posterior longitudinal ligament (OPLL) and multilevel spondylosis.[5] Laminoplasty can be single (open), closed door, muscle sparing and en bloc. It cannot be used in unstable or kyphotic spines. Suda *et al*. showed that if the local kyphosis in the cervical spine is upto <13, laminoplasty is the treatment of choice with excellent outcome.[6]

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The surgical treatment of CSM has evolved over several decades.[7] Posterior decompression is one of the most common surgical interventions for CSM.[8] Although laminoplasty is an established procedure and good long-term results have been reported, postoperative axial neck pain, decrease in lordosis, and range of motion (ROM) are observed in many patients.[7,8] Some scholars considered these complications to be the result of surgical damage to the spinous process-ligament complexes and injury to, and even complete resection of deep extensor muscles. Several minimally invasive spinal procedures for the cervical spine have been reported in recent years, but the conventional laminoplasty remains the gold standard.[8]

The objective of this study was to establish the effectiveness of laminoplasty for multiple level cervical myelopathy, by determining the improvement in the pre-operative JOA score.

METHODOLOGY

This study was descriptive study being conducted in the Department of Neurosurgery Unit II, Lahore General Hospital from June, 2014 to October, 2016. Patients who presented with upper and lower limbs weakness, sensory loss, paresthesia along with paralysis and JOA score of <12 which persisted for more than 6 months, were included.

The collected data were entered in SPSS computer software version 16 and analysed. Quantitative variables,

e.g. age and JOA score were calculated as mean and standard deviation. Qualitative variables like gender and postoperative incidence of kyphosis were presented as frequencies and percentages.

After an informed consent and anesthetic evaluation, all patients were subjected to laminoplasty. Patient was placed in the prone position with head fixed in a 3-pin Mayfield head clamp with slight flexion of the neck. A 2-finger breadth space was left between the neck and sternum. After giving a midline skin incision, the interspinous ligaments and muscles were separated at the interspaces superior and inferior to the laminoplasty level.

A bone nibbler was used to remove the spinous processes from C3-C6. C7 was undercut but the muscular and ligamentous attachments were saved. The junction between the lamina and facet was identified, where a high speed burr was used to create an opening of approximately 3mm. This required approximately 15% resection of the facet joint. The open side was drilled down to thin the lamina to the ligamentum flavum, while avoiding contact with the dura. Attention was turned to the hinge side, where a high speed burr was used to remove the dorsal cortex and to further thinning the ventral cortex. This trough was kept unicortical. On the open side, opening was performed by placing curved curettes underneath the lamina and gently manipulating it to the contralateral side. The ligamentum flavum was resected from C3-C7. Mini-plates of appropriate sizes were fixed. Intraoperative fluoroscopy was used to determine proper placement of hardware. The wound was copiously irrigated and closed. A soft cervical collar was applied. Gentle range of motion exercises were encouraged in the immediate postoperative period.

Patients were typically discharged 24-48 hours after surgery. X-rays were obtained at 4 weeks postoperatively to demonstrate adequate fixation. Active resistive exercises were begun at the 4-week postoperative time. The studied variables included JOA score (Table I), kyphotic deformity, and postoperative complications.

Table I: JOA score for evaluation of cervical myelopathy.

Section score	Points
(I) Upper extremity function	
Inability to eat with either chopsticks or spoon	0
Able to eat with spoon, but not with chopsticks	1
Able to eat with chopsticks, but inadequate	2
Able to eat with chopsticks, but awkward	3
Normal	4
(II) Lower extremity function	
Inability to walk	0
Require cane or aid on flat ground	1
Require cane or aid on stairs	2
Possible to walk without cane or aids, but slow	3
Normal	4
(III) Sensory	
Upper extremity	
Apparent sensory loss	0
Minimal sensory loss	1
Normal	2
Lower extremity	
Apparent sensory loss	0
Minimal sensory loss	1
Normal	2
Trunk	
Apparent sensory loss	0
Minimal sensory loss	1
Normal	2
(IV) Bladder function	
Urinary incontinence or retention	0
Severe dysuria (sense of retention, straining)	1
Slight dysuria (pollakiuria, retardation)	2
Normal	3

RESULTS

Thirty-six patients were included in the study. The mean age of patients was 56.32 ±5.16 years. Most of the patients were in the age group of 35 to 55 years (n=20, 56%) followed by 65 to 80 years (n=16, 44%). Twenty-four (67%) patients were males and 12 (33%) female; and male to female ratio was 2:1. Thirty-three (92%) patients did not have kyphotic deformity, while only 3 (8%) patients developed kyphotic deformity.

All patients did extremely well after laminoplasty (Figures 2 and 3). According to JOA score, out of 32 patients, 3 (9%) patients remained static, while 1 (3%) patient has slight deterioration which gradually improved with physiotherapy in almost 6 months time. One patient developed deterioration of JOA score immediately postoperatively. He also developed wound infection along with CSF leak. His wound was explored and a graft from the fascia lata was applied; fibrin glue was used to block the CSF leak.

Although the CSF leak of the patient subsided and wound was healed within few weeks after surgery, but his JOA scored remained at the preoperative status. Three patients developed postoperative kyphotic deformity, which settled in all of them in 3 months time.

Postoperative radiological studies showed marked increase in the axial diameter of the spine.

DISCUSSION

This study was descriptive study for patients having myelopathy due to involvement of multiple cervical levels. In all patients, cervical spine X-rays of anterio-posterior, and lateral views were performed to address the primary pathology and also to rule out kyphotic deformity.

Symptoms of CSM are headaches, typically occipital ones, tinnitus, progressive neck pain, and Lhermitte's sign.[8,9] Similar signs and symptoms were encountered in these patients. Murali reported that the incidence of postoperative kyphosis ranges from 2% to 4%. Cervical

Figure 1: Follow-up JOA scoring system.

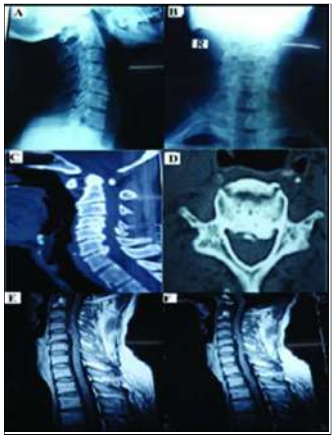

Figure 2: Preoperative images: (A) X-ray cervical spine lateral view; normal lordotic curvature. (B) X-ray AP view showing degenerative changes with osteophytes and facet joint arthrosis. (C) CT scan saggital view showing osteophytes & reduced disc height. (D) CT axial view showing degenerative changes along with canal diameter compromise. (E & F) MRI Sagittal view showing growth of osteophytes and herniated disc.

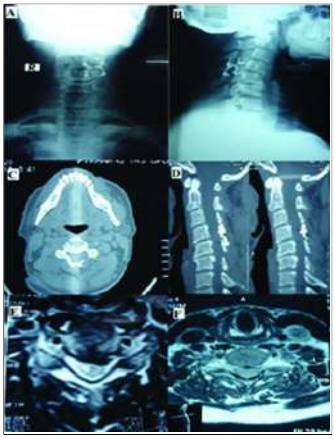

Figure 3: Postoperative images: (A) X-ray AP view. (B) Lateral view showing the mini plates in position. (C) Postoperative CT scan showing the mini plates and the increase in the axial diameter of the canal. (D) Axial CT scan showing cervical stenosis. (E & F) Postoperative axial MRI scans showing axial diameter widening after open door laminoplasty.

range of motion has been reported to reduce from 17-50%, with an average of approximately 50% after laminoplasty.[8,9] A very small 0.056% patients in this study developed wound infection secondary to CSF leak, which is in accordance with another international study in which the reported incidence of infection was 1.57%.

Mostly, patients have combination of upper motor neuron symptoms in the lower extremity and lower motor neuron signs in the upper extremity. Patients present with gait dysfunction due to ataxia, hypertonicity, muscle control deficiencies and weakness.[4] Most of these patients also had combination of both upper and lower motor neuron symptoms in all the limbs and also presented with bladder dysfunction. The incidence of CSM is more common in men.[4,10] In men, it is presented in 13% by the third decade and in 100% over the age of 70 years.[10] However, in women, it occurs in later life. Degenerative spondylosis is the common cause if it presents later in life.[12] In line with other studies, male gender was predominant (n=24) in this study, while female patients were only 12 and their presentation was in later age.

The dire and devastating nature of the clinical course validates decompression of cord surgically. Posterior decompression has been described as a treatment for CSM since the 1940s.[11,12,14] This study also advocated the posterior approach that is laminoplasty as a preferred and safe procedure.

MR imaging is the main stay in the evaluation of cervical myelopathy. In this case, T2-weighted sagittal images illustrated compressive features due to cervical spondylosis. CT scan showed ossified ligaments. CT is more of use when a high probability of bony injury deformity or ligamentous calcification is present.[11,12] In this study, MRI cervical spine was done in every case to evaluate the exact location of the pathology and the involvement of the spinal cord at multiple levels.

CT scan of the cervical spine sagittal and axial views was done for identifying the calcified ligaments and assessing the axial compromise of the canal on the axial cuts in this study. The myelopathy of cervical spine involves static factors as well as dynamic factors.[13] Static factors include developmental or acquired spinal canal stenosis in cervical region, while dynamic factors include repetitive insult to the cervical cord.[13,14] Hence, these mechanical factors result in direct injury to neurons and glia and a secondary cascade of events including excitotoxicity, apoptosis and ischemia; a pathophysiology analogous to that taking place in traumatic spinal cord injury.[15]

Cervical myelopathy outcome is assessed by JOA score. Maximum score (normal function) is 17. Miyazaki *et al*. noted that improved neurologic status was preserved at a mean of 12 years postoperatively.[18] Yosho *et al*. reported in his study that the mean JOA score before surgery was 10.1 ±3.0 and improved significantly to 12.9 ±2.7 at 1 year after surgery.[17] In this study, 83.3% patients did extremely well where the JOA score in them improved postoperatively. Only three (16.67%) patients in this study developed postoperative kyphotic deformity, which settled within three months in all of them with increased cervical ROMs.

Postoperative radiology also confirmed increase in axial diameter of cervical spine. Hamburger *et al*. stated that patients with postoperative axial canal area more than 160 mm^2 achieved a good result and recommended a surgical plan to achieve this target area.[16]

CONCLUSION

Laminoplasty is the treatment option for spondylotic cervical myelopathy. Cervical laminoplasty remains an unswerving modus operandi for decompressing the spine posteriorly, but the most favourable technique for the cervical myelopathy ought to take into consideration both the patient's health and the characteristics of the disease, along with the expertise of the surgeon. Laminoplasty minimises the risk of graft and fusion

related complications, post-op kyphosis and instability, and morbidity of anterior approach.

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Spectrum of Joint Deformities in Children with Juvenile Idiopathic Arthritis

Samia Naz[1], Misbah Asif[2], Farrah Naz[1], Hina Farooq[3] and Muhammad Haroon Hamid[1]

ABSTRACT

Objective: To determine the frequency and types of joint deformities in children with juvenile idiopathic arthritis and their association with clinical parameters and rheumatoid factor.

Study Design: Cross-sectional study.

Place and Duration of Study: Rheumatology Outpatient Clinic, the Children's Hospital and the Institute of Child Health, Lahore, from September 2014 to February 2015.

Methodology: All patients of both genders of less than 16 years of age, who fulfilled the International League of Association for Rheumatology (ILAR) criteria for Juvenile Idiopathic Arthritis (JIA), were enrolled in this study. Their demographic data, duration of disease at the time of presentation, types of JIA, various joint deformities and rheumatoid factor (RF) were documented. Statistical analysis of data was done on SPSS version 16. Chi-square test was applied to determine the association of clinical deformity with age of patients, disease duration at presentation, types of JIA and RF.

Results: Out of 70 patients enrolled during the study period, 51.4% were boys with mean age at presentation being 9.44 ±3.89 years (2-7 years) and median duration of disease being 24 months (interquartile range 42 months). Forty patients (57.1%) had joint deformities. Most common joints involved were hand (50%), wrist (50%), and knee (35.7%). The common types of joint deformities were boutonniere deformity (28.6%), ulnar deviation of wrist (28.6%), fixed flexion deformity of wrist (22.9%), and knee (31.4%). The most common type of JIA was polyarthritis RF negative with or without deformity. There was a strong association of deformities with older age of patients at presentation (p=0.036), longer duration of disease at presentation (p=0.028), polyarthritis (RF seronegative / seropositive) (p=0.013), and seropositivity (p=0.04).

Conclusion: More than 50% patients with JIA have joint deformities. Joint deformities are more likely to be seen in children with long-standing disease, those with polyarthritis JIA and seropositive patients.

Key Words: *Juvenile idiopathic arthritis. JIA. Joint deformity. Polyarthritis. Rheumatoid factor (RF).*

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the leading cause of autoimmune arthritis in children and adolescents causing clinical deformities. Epidemiological studies have reported a burden of 0.07-4.01 per 1000 children.[1] The true incidence and prevalence in our region is not known. There are substantial geographic, and ethnic differences are present regarding the frequencies of different types, age at onset, and immunological markers.[1-3]

JIA has different subtypes with varied morbidity. It is a significant cause of short- and long-term disability in children and adolescents.[1,4] The most serious complication is the development of joint deformities. Common deformities of hand and wrist joints include spindling of fingers, swan neck deformity, boutonniere deformity, Z-deformity of thumb, subluxation of metacarpophalangeal joints, ulnar deviation of wrist, radial deviation of fingers, and flexion/fixed flexion deformity of wrist. Feet and ankle deformities are lateral deviation of big toe (*hallux valgus*), subluxation of metatarsophalangeal joints and valgus deformity of ankle. Knee deformities in JIA are *valgus* and *varus* deformities and flexion/fixed flexion deformity. Atlantoaxial subluxtion is the deformity of cervical spine. Other orthopedic complications include leg length discrepancy and growth delay.[5]

JIA is a chronic disease causing deformities; and timely diagnosis and prompt multi-disciplinary management is necessary to prevent complications. Various studies have shown different early predictors of poor outcome including female gender, older age at onset, longer duration of disease before referral, early involvement of small joints of hands and feet, rapid appearance of erosions, unremitting inflammatory activity, RF seropositivity, and subcutaneous nodules.[6] There is paucity of reported literature from Pakistan on this deforming chronic ailment in children, especially in the context of spectrum of deformities and its possible associations.

The objective of this study was to determine the frequencies and types of joint deformities in juvenile

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idiopathic arthritis and their association with clinical parameters and rheumatoid factor.

METHODOLOGY

This cross-sectional analytical study was carried out at Rheumatology Outpatient Clinic, The Children's Hospital and The Institute of Child Health, Lahore, from September 2014 to February 2015. Informed consent was obtained from all parents or children. All patients seen in clinic during the study period, of both genders of less than 16 years of age who fulfilled the International League of Association for Rheumatology (ILAR) criteria for Juvenile Idiopathic Arthritis (JIA),[5] were enrolled in this study. Their demographic data, duration of disease at presentation, and types of arthritis per ILAR criteria were recorded in a pretested proforma at their first clinical visit. The ILAR criteria included the following:

1. Systemic-onset JIA, arthritis in ≥1 joints with or preceded by fever of at least 2 weeks in duration that is documented to be daily ("quotidian") for at least 3 days and accompanied by ≥1 of the following: (a) evanescent (nonfixed) erythematous rash, (b) generalised lymph node enlargement, (c) hepatomegaly or splenomegaly or both, and (d) serositis.

2. Oligoarticular JIA, arthritis affecting 1-4 joints during the initial six months of disease. Two subcategories are recognised as persistent oligoarthritis-affecting ≥4 joints throughout the disease course, and extended oligoarthritis-affecting ≥4 joints after the first 6 months of disease.

3. Rheumatoid factor negative polyarthritis, arthritis affecting ≥5 joints during the initial six months of disease and a test for RF is negative.

4. Rheumatoid factor positive polyarthritis, arthritis affecting ≥5 joints during the initial six month of disease and 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive.

5. Psoriatic arthritis, arthritis and psoriasis, or arthritis and at least 2 of the following: (a) dactylitis, (b) nail pitting and onycholysis, (c) psoriasis in a first-degree relative.

6. Enthesitis-related arthritis, arthritis and enthesitis, or arthritis or enthesitis with at least two of the following: a. presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain; b. presence of HLA-B27 antigen; c. onset of arthritis in a male over 6 years of age; d. acute (symptomatic) anterior uveitis; and e. history of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis in a first-degree relative.

7. Undifferentiated arthritis is arthritis that fulfils criteria in no category or in ≥2 of the above categories.[5]

Patients were thoroughly examined for various deformities of joints. Deformities involving wrists, elbows, knees, and ankles were taken as one, either single or both joints were involved respectively. Upper limb deformities noted included spindling of fingers, swan neck deformity, boutonniere deformity, Z-deformity of thumb, ulnar deviation of wrist, radial deviation of finger, and flexion/fixed flexion deformity of elbow joint. Lower limb deformities noted included flexion/fixed flexion deformity of knees, *valgus* deformity of knees and ankles, *varus* deformity of knees, lateral deviation of toes, and outward deviation of feet. Rheumatoid factor was determined by indirect haemagglutination method.

Statistical analysis was performed by statistical package for social sciences (SPSS) version 16.0. Mean and median were determined for quantitative variables. Frequencies and percentages were used to describe distribution of age and gender in different groups. Frequency of deformities in various joints of body is described as pie chart. Various types of deformities in upper and lower limbs are shown as bar charts. Chi-square test was performed to determine the relationship of demographic data and rheumatoid factor with joint deformity. P-value of ≤0.05 was considered statistically significant. Relationship of joint deformities with age, duration of disease at presentation, types of arthritis, and RF is described in tabulated form.

RESULTS

Out of 70 patients enrolled, 40 (57.1%) were with clinical joint deformities. Among all, 51.4% (n=36) were male and mean age at presentation was 9.44 ±3.89 years (range 2-17 years). Distribution of age at presentation in various subgroups showed that 8 patients (11.4%) were less than 5 years of age, 32 patients (45.7%) were of 5-10 years, 23 patients (32.9%) were between 11-15 years of age and 7 patients (10%) were more than 15 years of age.

Median duration of disease at presentation was 24 months with interquartile range 42 months. Distribution of disease duration at presentation showed that 23 patients (32.9%) were presented within 12 months of disease onset, 26 patients (37.1%) between 12-36 months of disease onset, and 21 patients (30.0%) were presented after 36 months after disease onset.

Distribution among different subtypes of JIA showed RF-negative polyarthritis in 43 patients (61.4%), RF-positive polyarthritis in 5 patients (7.1%), systemic onset disease in 14 patients (20%), and oligoarticular arthritis in 8 patients (11.4%).

Out of 85 deformities noted in 70 patients, hand and wrist were the commonest (50%), followed by knee joint, feet and ankle joint and cervical spine involvement. Distribution of various joint deformities is shown in Figure 1.

In upper limb, boutonniere deformity and ulnar deviation of wrist were the commonest deformity, (Figure 2a);

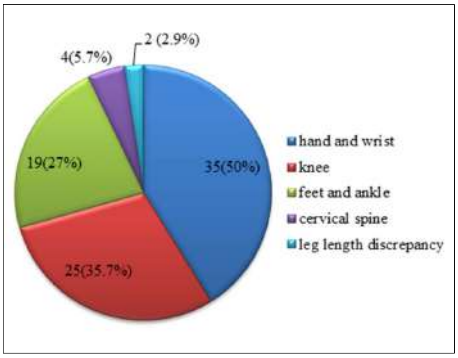

Figure 1: Distribution of frequency of deformities in various joints of body.

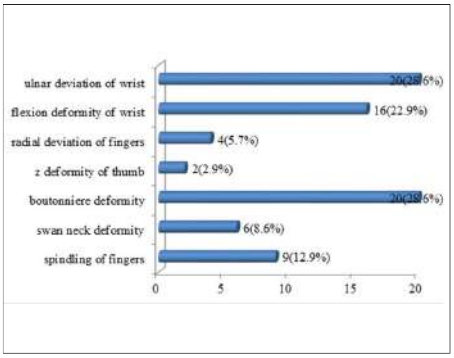

Figure 2a: Types of upper limb deformities

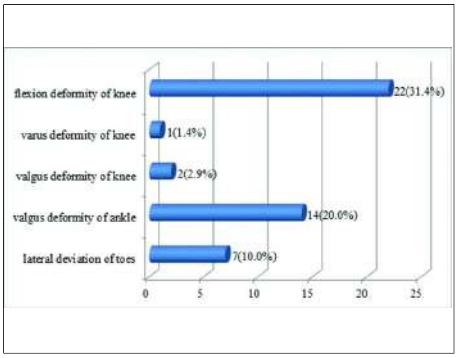

Figure 2b: Types of lower limb deformities.

Table I: Relationship of deformity with ages of patients, duration of illness, types of JIA, and RA factor (n=70).

	JIA patients			
	With deformity	Without deformity	Total	p-value
	40 (57.1%)	30 (42.9%)	70 (100%)	
Age of patient				
Less than 5 years	1 (2.5%)	7 (23.3%)	8 (11.4%)	0.036
5- 10 years	18 (45%)	14 (46.7%)	32 (45.7%)	
11-15 years	16 (40%)	7 (23.3%)	23 (32.9%)	
More than15 years	5 (12.5%)	2 (6.7%)	7 (10%)	
Duration of illness				
<12 months	8 (20%)	15 (50%)	23 (32.9%)	0.028
12-36 months	17 (42.5%)	9 (30%)	26 (37.1%)	
>36 months	15 (37.5%)	6 (20%)	21 (30%)	
Types of JIA				
Oligoarticular JIA	3 (7.5%)	5 (16.7%)	8 (11.4%)	0.013
Systemic onset JIA	4 (10%)	10 (33.3%)	14 (20%)	
Rheumatoid factor (RF) positive polyarthritis	5 (12.5%)	0 (0%)	5 (7.1%)	
Rheumatoid factor (RF) negative polyarthritis	28 (70%)	15 (50%)	43 (61.4%)	
RA factor				
RA factor positive	5 (12.5%)	0 (0%)	5 (7.1%)	0.044
RA factor negative	35 (87.5%)	30 (100%)	65 (92.9%)	

while in lower limb, the most common deformity was flexion deformity of knee (Figure 2b).

Data was stratified according to age and gender. Chi-square test was applied to determine the relationship of joint deformities with age and gender of patients, duration of disease at presentation, types of JIA, and seropositivity. It was found that older age of patient at presentation (p=0.036), prolonged duration of illness at presentation (p=0.028), polyarthritis (p=0.013), and seropositivity (p=0.044) were significantly associated with joint deformities (Table I).

DISCUSSION

Juvenile idiopathic arthritis in childhood is the commonest disease leading to childhood morbidity in terms of joint deformities. Despite improved awareness of the disease and expanded treatment options, about 50% of patients enter their adulthood with active arthritis, ongoing joint destruction and a decreased quality of life.[5-7] The actual incidence of deformities in children is not well documented; but in an adult study, the frequency of hand deformities was reported in patients up to 60%.[8]

Among all patients with JIA, female outnumbered male as described in Western literature. In this study, male and female were almost equal in number. Late age at presentation was found, which was also reported in many studies from South East Asia.[9-11] Another study conducted by Gowa *et al*. from Karachi described 55% female, and 85% presented between 6-10 years of age.[12] All these studies are hospital-based and conducted in same geographic location.

Polyarticular JIA was the most frequent type seen in this study. This is consistent with many studies from Pakistan and India.[9,10,11,13] Whereas, oligoarticular JIA and systemic onset disease were more common types in other studies from West.[3,14-16] The reason may be the biological characteristics of the disease or ethnic and geographic similarity of both populations in this subcontinent. In addition, there are different classification criteria used in different studies and making it difficult to compare these studies with each other.

It is known that patients presenting late after disease onset are at higher risk of deformities and functional disabilities as compared to those presented early and managed aggressively.[1,5,7,10] Late referrals may be due to little knowledge of the disease at patient as well as at primary physician level.

In this study, most common finger deformities were boutonniere deformity and swan neck deformity. These results are closely related to other studies which stated that swan neck and boutonniere deformities are the two most common afflictions of interphalangeal joints.[6,8,17] While, Zakrzewska *et al*. reported that swan neck deformity was found in all age groups and boutonniere deformity was seen only in older age groups.[18] It has been found in this study that patients with JIA had both radial and ulnar deviation of wrist. This is consistent with another study.[18] Frequency of ulnar deviation is 28.6% in this study. Johnsons *et al*. from Sweden showed that ulnar deviation of wrist was the commonest deformity in

44% of patients.[8] The reason of such a high frequency of ulnar deviation of wrist may be due to age difference between the two study groups as Johnson *et al*. conducted his study in adults with rheumatoid arthritis.

CONCLUSION

Juvenile idiopathic arthritis is associated with multiple deformities in more than half of patients with JIA. Among these deformities, hand and wrist are the commonest involved joints followed by knee joints. These deformities are statistically significantly associated with polyarthritis, seropositivity, and late presentation of patients to tertiary care centre. Early referral to tertiary care hospital and appropriate management may decrease the frequency of such deformities in children with JIA.

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Prolonged and Increased Usage of a Flexible Ureterorenoscope: The Maelor FURS Protocol

Muhammad Iqbal[1], Rachel Jones[1], Stephen F. Hughes[2] and Iqbal S. Shergill[1,2]

ABSTRACT

We present our point of technique detailing the specific preoperative and postoperative steps used in our institution to prolong the use of a flexible ureterorenoscope, and discuss the potential cost-effectiveness of this protocol. We have used a single flexible ureterorenoscope, for 145 consecutive cases to date, using the protocol described in this article. This prolonged use has resulted in a calculated cost per case of £273.48 GBP. We have described our experience of a dedicated protocol to prolong the usage of a single flexible ureterorenoscope. We would consider recommending the technique described in this article, to prolong flexible ureterorenoscope usage in a cost-effective manner.

Key Words: *Flexi ureterorenoscope. Laser lithotripsy. Maelor protocol.*

INTRODUCTION

Flexible Ureterorenoscopy (FURS) is increasingly used worldwide, allowing effective treatment of stones in all calyces using a single procedure, with a high stone-free rate, as well as being able to diagnose and effectively treat upper tract transitional cell cancer. However, because of their fragile nature, FURS can be associated with high costs due to damage, resulting in repair or replacement. Several reports of optimum perioperative care to prolong usage have been described.[1,2] But to our knowledge, very little data exists about preoperative and postoperative care. This article describes the use of a dedicated protocol, including specific preoperative and postoperative steps, for prolonged usage of FURS at our institution. We also describe the cost-effectiveness data generated, because of this protocol.

Presentation of Technique: At our institution, since March 2015, we strictly introduced technique called Maelor FURS protocol for all upper tract stone and TCC cases, using the Olympus P6 flexible ureterorenoscope. until March 2017, using the following steps in the protocol, the same scope has been used for 145 consecutive cases.

Preoperative Protocol: The Olympus P6 scope is only handled by educated and trained senior nurses, who have undergone a formal protocol driven programme and subsequent competency verification, at our institution. The scope is stored in a dedicated room which is 5x2 feet wide, containing a cleaning unit and a drying cupboard, where the scope can be hanged at built-in hooks (Figure 1).

When required for a urological procedure, the pre-cleaned scope is transported in a sterile device, containing a sterile plastic bag wide enough to accommodate large coiled loops.

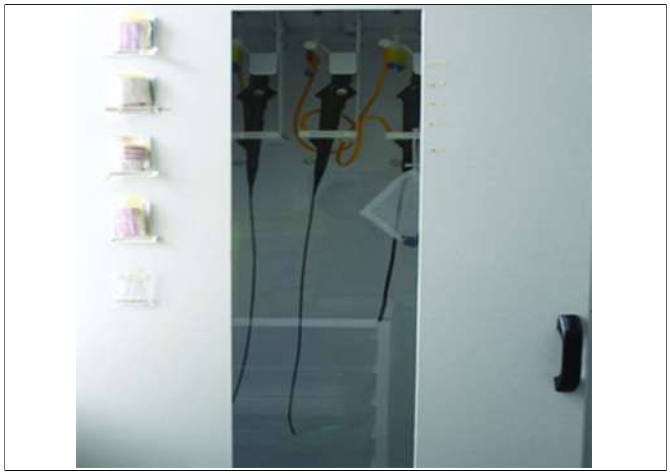

Figure 1: Cupboard with hanging scopies.

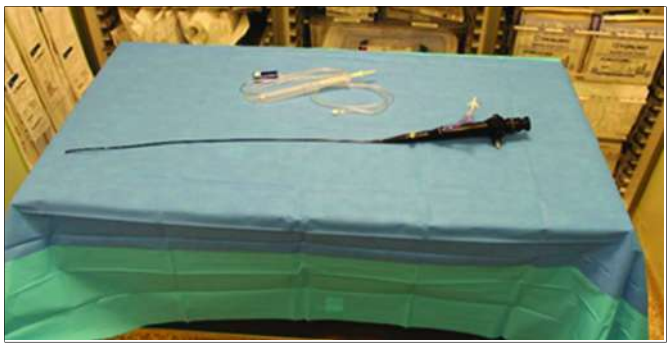

Figure 2: Scope on trolley.

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Perioperative Protocol: Once ready to be used, the scope is taken out of the container onto a sterile instrument trolley, which is 4x3 feet long covered by a sterile waterproof sheet. The scope is always kept straight on the trolley, including connecting light guide cable, camera head and irrigation tubing, to avoid any inadvertent damage (Figure 2).

Commonly described perioperative steps in the urological literature are used during the procedure, and whenever the scope is not in use, it is always transferred back onto the trolley.[3]

Postoperative Protocol: Once the urological procedure has been completed, a standard operating protocol is used, by a senior nurse, including guidelines for transportation, cleaning and storage. Precleaning is performed before transfer to the decontamination room. The exterior surface of the scope is washed with soft cloth soaked with cleaning solution, and the working channels are flushed with solution and air. The pre-cleaned scope is then transferred to the decontaminated area, keeping the scope moist but not submerged in liquid during transport. A leak test is performed by removing all port covers and fiction valves, and the scope is then pressurised to the recommended pressure. Pressure is maintained, and the scope is inspected for minimum 30 seconds. Scope processing is performed in dedicated room with uni-directional workflow to clean area and the door closed all the time. Processing is performed by a senior trained nurse, who has received education and competency verification activity related to scope cleaning. All precautions including surgical mask with eye protection, fluid resistant gown, surgical gloves and fluid-proof shoe covers are employed. The scope is manually cleaned with cleaning solution, including the working channel. The exterior surface and channels are then dried with instrument air. Inspection of the cleaned scope for cleanliness, missing parts, lens clarity, integrity of seal and gaskets, any physical or chemical damage, moistures and functions, is then performed. The inspected scope is then exposed to high level disinfectant and sterilisation, with care taken that the scope is in complete contact with the solution. After disinfection, the scope is rinsed with sterile water and then dried, using a mechanical processing drying system. The scope is then stored in the drying cupboard with sufficient height, width and depth to allow scope to hang vertically without coiling and not touching the cabinet bottom (Figure 1). The scope is stored with all valves opened and clear cue to identify a clean scope ready for use. The scope is sent for routine service after a cycle of 25 cases.

The described Maelor FURS protocol, incorporating strict preoperative and postoperative steps, represents a potentially cost-effective method to prolong life of a flexible ureterorenoscope.

Table I: Cost-effectiveness data, using Maelor FURS protocol.

Number of uses	Overall cost (GBP)	Cost per case (GBP)
25	£18,091.00 (12700 + 5391)	£723.64
50	23,482.00 12700 + (2 x 5391)	£469.94
100	£34,264.00 12700 + (4 x 5391)	£342.64
145	£39,655.00 12700 + (5 x 5391)	£273.48

RESULTS

We have performed 145 cases from March 2015 to March 2017. As such, and if an average cost of Olympus P-6 URS at £12700 GBP is used, and the service cost contract (per 25 cases) at £5391 GBP, the cost per case has been calculated as £273.48 (Table I).

DISCUSSION

While several reports in the literature have discussed specific perioperative steps to increase the life of a flexible ureterorenoscope, in this article we have described our experience of a dedicated protocol to prolong the usage of a single flexible ureterorenoscope, the Maelor FURS protocol. This involves a series of very specific and comprehensive preoperative and postoperative care steps, which we believe, in addition to the well described perioperative steps in the urological literature, further prolong the life of a modern flexible ureterorenoscope.[4] Working in a district general hospital, the pressure on costs and repair/replacement is very significant. As such, it is extremely reassuring that using our protocol, the average cost was relatively low, at £273.48 per case. We would consider recommending the technique described in this article, to prolong flexible ureterorenoscope usage in a cost-effective manner.

CONCLUSION

We conclude that by using Maelor FURS protocol, the life span of FURS can be prolonged, which ultimately resulted in cost-effectiveness. We strongly recommend Maelor FURS protocol to be incorporated for providing quality care and cost benefit for trust.

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Aesthetically Characterized Ocular Prosthesis

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ABSTRACT

Loss of eye has immense intimidating impact on social life of a patient. Ocular prosthesis can be stock prosthesis, or it can be customized according to the patient's socket tissue bed and his/her individualized aesthetic requirements. There are many methods of improving aesthetics of the ocular prosthesis, from painting the sclera and iris, use of transparent grids for proper orientation up to the use of digital photographic image of contra-lateral normal eye. Present case report demonstrates a new method of enhancing the aesthetics of an eye prosthesis using silk fibers which are easily available.

Key Words: *Eye defect. Customized ocular prosthesis. Silk fibers.*

INTRODUCTION

Among the various defects, evisceration and enucleation are the most common surgical defects of the eye. In evisceration, sclera and extraocular muscles are left intact and is frequently reported as a cosmetic procedure; whereas in enucleation, surgeon removes the whole eyeball.[1]

Loss of eye has great disheartening impact on social life of a patient. It significantly affects the individual's physical, psychological, emotional and social well being.[2] For an aesthetic and retentive effect, a multidisciplinary approach including a prosthodontist, ophthalmologist, surgeon and maxillofacial prosthetist should be included.[3]

It is the moral responsibility of a prosthodontist to give a natural looking prosthesis to the patient, which helps him or her to overcome this agony. Ocular prosthesis can be stock prosthesis, or it can be customized according to the patient's socket tissue bed and his/her individualized aesthetic requirements.[4] Aesthetic fabrication of ocular prosthesis has always been a challenge to a prosthodontist. This is a case report of a patient with left eye phthisis bulbi, rehabilitated by a custom-made sclera shell.

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CASE REPORT

An 18-year girl presented to the Department of Prosthodontics, Government Dental College (GDC), Indore, referred from another hospital, with chief complaint of poor facial appearance due to missing left eye (Figure 1). Patient had local eye infection at the age of 3-year, which was overlooked by her parents due to illiteracy and poor socioeconomic status. After 1 year, patient started losing her eyesight and was diagnosed as pthisis bulbi. Later, evisceration of the eye was carried out.

As the patient was devoid of any prosthesis from childhood, the size of the eye socket was relatively very small compared to the normal side. A thorough clinical examination of the eye socket was carried out. On palpation, it was found that there was no associated pain, discomfort or residual edema. The movements of rudimentary eyeball were intact.

Appropriate treatment was planned and it was decided to fabricate custom-made eye prosthesis. The whole procedure regarding the fabrication of the prosthesis, including its maintenance and limitations, was explained to the patient.

A primary impression of the eye socket was made with irreversible hydrocolloid impression material with autopolymerising acrylic stock tray and syringe. The cast was obtained by pouring the impression with two pour technique (Figure 2). A wax pattern with properly oriented iris was tried and finalized (Figure 3). As the patient had tortuous scleral vessels, it was not possible to duplicate them in prosthesis with any conventional technique and this would have made the prosthesis appear more artificial. Hence, it was decided to incorporate silk fibers in the scleral part of the prosthesis. A pair of silk threads (Anchor Silks, Mumbai, India) was selected matching the colour of patient's scleral vessels. A sliver of silk thread was shredded with the scalpel to yield an aggregate of fine flocules (Figure 4). Conventional dewaxing of the wax pattern was carried out. After cooling of the flask, separating medium (Acralyn-H, Asian Acrylates, Mumbai, India) was painted on the dental stone, both on

Figure 1: Patient with eviscerated left eye.

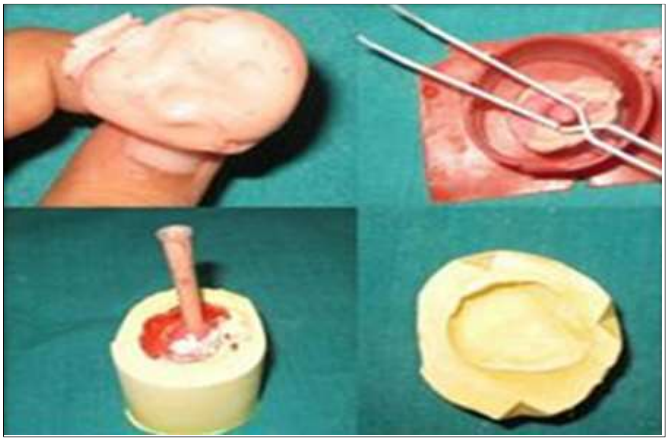

Figure 2: Impression and cast of the eye.

Figure 3: Wax pattern try-in.

Figure 4: Silk fibers selection.

Figure 5: Final eye prosthesis.

Figure 6: Patient's frontal view before and after placement of the eye prosthesis.

tissue and on polished surfaces. Care was taken not to wet the iris in the counterflask. Sufficient amounts of clear and 'D' shade heat cure poly methyl methacrylate (PMMA) material (DPI-Heat Cure, dental products of india, Mumbai,) were mixed in two separate dappen dishes with 3:1 powder to liquid ratio. Small amount of clear heat cure PMMA material was spread over the counterflask containing iris in its late stringy stage. Clumps of silk fibers, which were already prepared, were spread over the corresponding location; red fibers along inner canthus side of the prosthesis and yellow fibers along the inferior part of the sclera. 'D' shade heat cure PMMA, which was in its doughy stage, was packed in the remaining portion of the flask and it was bench pressed. Conventional curing was carried out and prosthesis was retrieved from the flask. The appropriately finished and polished prosthesis was inserted into the socket after being disinfected and lubricated with an ophthalmic lubricant (Lacrigel, Sunway Pvt Ltd, Mumbai, India) to sustain a tear film over the prosthesis and to improve eye movements (Figures 5 and 6). Inconsequential adjustments were made at the time of insertion as per the patient's comfort and aesthetics. Instructions were given to the patient regarding proper care and hygiene maintenance techniques in order to facilitate successful adaptation of the prosthesis; and the need for regular recall appointments was emphasized. Instructions on the use of ancillary products and procedures were also given in order to help the patient adapt to the prosthesis.

DISCUSSION

Fabrication of ocular prosthesis has been known to human being since times immemorial.[5] Prosthetic rehabilitation of patient with missing eye not only improves aesthetic appearance, but also enhances self-confidence and social acceptance of the patient. Along with the aesthetic, retention of the eye prosthesis is very important for the comfort of the patient. A variety of methods of auxiliary retention for eye prostheses include eyeglasses, engagement of hard and soft tissue undercuts,[6,7] magnets, adhesives, combinations of the above,[6] and osseointegrated implants.[8] The very frequently used conventional methods to retain orbital prostheses are the eyeglass frames and anatomic retentive undercuts.[9] In the present case, anatomic undercuts were used for the retention of the eye prosthesis. There are many methods of improving aesthetics of the ocular prosthesis, from painting the sclera and iris, use of transparent grids for proper

orientation up to the use of digital photographic image of contralateral normal eye.[10] Stock eye shells are available in many colours and shades in the market. Many times a close match always occurs with normal side iris. But scleral match is difficult to obtain, especially when the patient has tortuous arteriolar vessels in the sclera of the normal eye. In this case, patient had red clumps of arteriolar vessels at inner canthus portion of the sclera and yellow adipose tissue deposits inferior to iris. Incorporating similar color fibers in clusters has produced more natural looking prosthesis.

In literature, several impression materials, techniques, and retentive aids for the fabrication and retention of the ocular prosthesis have been described. The selection of the material and retentive aid mainly depends on the clinician's skill. Methods used for fabrication of the eye prosthesis should be simple and time saving. This clinical report is describing the simple method of fabricating the aesthetically fitting custom-made ocular prosthesis.

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CASE REPORT

Misplaced Central Venous Catheter in Carotid Artery during Emergency Surgery for the Total Correction of Tetralogy of Fallot of an Adolescent Boy

Syed Shabbir Ahmed, Faisal Junejo and Fazal Hameed Khan

ABSTRACT

Ultrasound-guided central venous cannulation is now considered as the standard of care, and this has largely replaced blind central venous cannulation using anatomical landmarks. We are reporting a case of inadvertent placement of central venous catheter in the right common carotid artery with the use of ultrasound guidance during emergency surgery for the total correction of Tetralogy of Fallot (ToF). This patient luckily had a favourable outcome despite this inadvertent catheter placement which was not recognised even after completion of surgery .The patient also received drug infusions of inotropes and vasopressors through this malplaced central line into the aorta. The possible mechanism, consequences, prevention and management of this inadvertent cannulation are discussed in this report.

Key Words: *Central venous catheter. Congenital heart surgery. Tetralogy of Fallot. Ultrasound.*

INTRODUCTION

It is recommended to use ultrasound (US) rather than using the landmark technique alone to pass central venous catheter (CVC).[1] The Agency for Healthcare Research and Quality of the USA and the UK National Institute of Clinical Excellence, both recommended CVC with US guidance as one of the safest practices to augment better patient care.[2] In our institute, we frequently use US for CVC insertion.[3] Tetralogy of Fallot (ToF) is the most common complex cyanotic congenital heart lesion. If the defect is not corrected at a younger age, then some of these patients later present with major aorto-pulmonary collateral arteries (MAPCAs). This is extremely rare; however, in areas where patients have limited access to surgical care, especially in developing countries like Pakistan, patients sometimes present with ToF along with MAPCAs.

CASE REPORT

A 15-year boy, who was a diagnosed case of ToF weighing approximately 40-45 kg, presented to the emergency department with history of cough, epistaxis, and hemoptysis. He was vitally stable. Hemoglobin was 18.9 g/dL with hematocrit of 58%. Platelet count was 172 x 109/L and oxygen saturation (SpO2) was 78% in room air. His transthoracic echocardiography showed ToF including severe pulmonary valve stenosis, and large conoventricular ventricular septal defect (VSD). Clinically, there was also a suspicion of major aorto-pulmonary collateral arteries (MAPCAs). He had massive hemoptysis resulting in aspiration of blood into the lungs. This resulted in respiratory distress, so he was intubated and mechanically ventilated. Later, he was resuscitated and moved to radiology for angioembolization. His CT showed mesh of collaterals arising from thoracic aorta supplying both lungs and pulmonary arteries. Some of these arteries were embolized. Bleeding settled, but he became severely hypoxic. His partial pressure of oxygen (PO_2) dropped to 34 mmHg from 70 mmHg on 100% fraction of inspired oxygen (FiO_2).

An emergency total correction was decided. CVC was inserted in internal jugular vein (IJV) under direct US guidance, but there was a clinical suspicion of arterial puncture in spite of the visualisation of needle in the vein, necessitating another attempt to be made with an 18G IV cannula, 7Fr multilumen CVC was inserted into the vein using Seldinger wire technique. Once the catheter was connected to the pressure transducer, arterial waveform tracing was observed with mean pressure between 45 and 53 mmHg. There was a strong suspicion that the central venous cannulation may have gone into the artery, but the fact that vein was punctured under direct US guidance and the assumption that right sided pressures are high due to more overriding of aorta resulted in confusion. There was no back flow of blood from the CVC lumen when a drip was attached to one of the ports. We started infusing fentanyl, atracurium, and tranexamic acid through this line. No abnormal findings were noted by the surgeons around aorta or during cross clamping of aorta. The defect was totally corrected and the patient was successfully weaned off from the

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cardiopulmonary bypass. After weaning, we started inotropes like epinephrine, milrinone, dopamine, and nitroglycerin as needed; and also gave calcium chloride, potassium chloride, heparin, and protamine through this line. The tracing did not get better even after successful operation, so a suspicion of inadvertent arterial canulation was made. Blood sample was withdrawn both from the radial artery catheter and the assumed central line. This confirmed that the central line has been misplaced in an artery as the PO2 of both the samples was 84 mm Hg. Chest X-ray done postoperatively in our cardiac intensive care unit (CICU), which clearly demonstrated that the line had gone inadvertently into the aorta. Another central line was passed through the right femoral vein, shifting all the drug infusions to this new central line.

Next morning patient was fully awake and responded to verbal commands, but unfortunately started to bleed again from the lungs. He was arrested and had a brief cardio-pulmonary resuscitation (CPR) and was revived. The chest tube had fresh blood, so patient was rushed to the operating room again. This time left thoracotomy and left lower lobectomy was done due to AV malformation and persistent bleeding from the left lower lobe. After this surgery, US of the neck was done to see the point of entrance of central catheter into the artery. It was revealed that the CVC pierced the posterior wall of right internal jugular vein and entered the right common carotid artery. As there was space available to compress the artery, so catheter was removed in the theatre and the pressure applied to the site of carotid puncture for 20 minutes. He remained hemodynamically stable after this episode, and was on ventilator for 24 hours; and then finally extubated. Patient was discharged after staying in the hospital for 20 days.

DISCUSSION

CVC is a routine procedure in cardiac surgery. Numerous complications are associated with CVC placement and selection of vein cannot be guaranteed to avoid complications, but appropriate use of technology with expertise is the key to avoid complications. Overall complication rate of 15% includes pneumothoax, hematoma, arterial puncture, hemothorax, infections, and thrombotic complications.[4] Mauricio and colleagues, showed that vein was located lateral to the artery in 24.3%, anterolateral in 33.8%, and anterior in 41.9%; and relation between IJV and carotid artery can be variable with the angle of rotation of neck. Arterial puncture was observed in 3-15% of central venous access procedures.[5,6] However, additional complications could be devastating, if it goes unrecognised and infusion continues in arterial system,[7] as happened in this case; where, all drugs were infused including blood products into the arterial system. According to our knowledge, it is the first case reported where all drugs were infused through arterial system during the whole procedure. Although some cases are reported here only for propofol infusion in arterial system in cardiac surgery.[7]

It is not known in this case how CVC went into carotid artery. It might have got punctured while threading CVC or while dilating with tissue dilator. An intraluminal position of the needle can be confirmed by observing the needle entering the vein with US guided access coupled with a steady flow of dark blood into the syringe. Bright red and high-pressure pulsatile bleeding is important, but imperfect clue to arterial puncture.[8] Dark, non-pulsatile backflow of blood may be seen with arterial puncture in the face of oxygen desaturation, hypotension, or needle malposition. If there is any doubt, the needle's location can be confirmed by pressure transduction. As an alternative, a blood gas sample can be drawn from the accessed venous site and compared with an arterial sample.[5,7] In our patient, arterial color of blood was already black because of ToF. Therefore, it was not reliable. On the other hand, the blood was slightly pulsatile when IJV was canulated but not found after placing CVC. It may be happened due to high hematocrait, we did not get much pulsatile blood. We did not transduce at any time before insertion of CVC, which should be considered. Blood or fluid flowing back into the CVC is another sign that may indicate an incorrect arterial CVC placement. Although this was not observed in our case because back flow was unlikely against infusion pump. So, whenever back flow is suspected, it should be checked without any external pressure by simply attaching it with un-pressurised fluid bag to flow freely. So, it is necessary to transduce or use manometer for waveform and pressure monitoring. We strongly agree with Weinberg and colleagues, in employing at least two safety methods to ensure the correct venous CVC placement, especially before starting an infusion. These include blood colour or backflow pulsatility, transduction of central pressure waveform, arterial blood gas analysis confirmation, and US confirmation of both the absence of the catheter in the artery and the presence of the catheter in the vein.[5] Transesophageal echocardiography (TEE) is used for many congenital heart operations. Catheter tips and guidewires are easily imaged with TEE, and one study demonstrated a 100% success rate for TEE-guided CVC placement in the superior vene cava (SVC) when TEE was used, versus 86% when surface anatomical landmarks were used in infants and children undergoing congenital heart surgery.[9] In our case, TEE was placed but not interpreted by a trained person. It was an emergency case, so things were not lined up. In our routine practice, only trained cardiologist or trained anesthetist in TEE are allowed to interpret. Therefore, knowledge of equipment like US and TEE is very important for interpretation.

Gentle traction followed by 20 minutes of local compression was applied to achieve haemostasis. This pull and pressure approach to manage a large bore carotid injury was retrospectively associated with higher complication rate and an immediate stroke risk of about 5.6%. In our case, pull and pressure approach was practised because of higher puncture site in the neck, which was easily accessible. It is worthwhile to go more caudally but should apply non-occlusive pressure which is not easy to monitor. Other available options are open repair or percutaneous device closure.[10]

In conclusion, inadvertent carotid artery CVC placement is a rare and potentially devastating complication, but it can be easily avoided by using multi-confirmatory approach during placement of CVC.

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The Asymptomatic Dissecting Aortic Aneurysm: An Incidental Finding on CT

Ateeque Ahmed Khan and Mahnoor Hafeez

ABSTRACT

We report a case of 65-year male patient, a known hypertensive and a chronic smoker, who presented to the Civil Hospital, Karachi with complaints of cough, hemoptysis and shortness of breath for three weeks. The chest radiograph showed left apical solitary pulmonary nodule (SPN) and aneurysmal dilatation of the descending thoracic aorta. He was further investigated with contrast enhanced computed tomography (CECT) scan of chest, which apart from demonstrating malignant pulmonary lesion, surprisingly revealed Stanford type B descending thoracic aortic dissecting aneurysm with intramural hematoma, jeopardising renal and splanchnic circulation. An asymptomatic dissecting aortic aneurysm is relatively rare. To the best of authors' knowledge, less than 15 case reports have been published in the international literature.

Key Words: *Aortic dissection. Stanford classification. Solitary pulmonary nodule. CT.*

INTRODUCTION

The dissection of aorta is a rare cardiovascular emergency that requires prompt diagnosis and management. CT allows diagnosis of the aortic dissection with a sensitivity and specificity of nearly 100%. According to Stanford classification, there are two subcategories of artic dissection; the one involving the ascending aorta is type A, and the other one distal to the left subclavian artery is type B. CT can also be used to diagnose atypical forms of aortic dissection such as intramural hematoma, penetrating atherosclerotic ulcer, rupture of the dissection, and atypical appearance of the intimal flap. It also plays a role in surveillance of life-threatening ischemic complications of abdominal branch vessels. Aortic dissection is a rare phenomenon, occurring at an estimated rate of three per 100,000 people per year. About 96% of individuals with aortic dissection present in an emergency setting with severe pain that had a sudden onset.[1,2]

We present a rare case of asymptomatic Stanford type B descending thoracic aortic dissecting aneurysm with intramural hematoma jeopardising renal and splanchnic circulation.

CASE REPORT

A 65-year male patient, a known hypertensive for the last eight years and a chronic smoker, presented to the Civil Hospital, Karachi with complaints of cough, hemoptysis and shortness of breath for three weeks. The patient denied any episode of chest or abdominal pain with normal bowel habits. He had no previous surgical history. Chest radiograph showed left apical solitary pulmonary nodule (SPN) and aneurysmal dilatation of the descending thoracic aorta (Figure 1). He was further investigated with contrast-enhanced computed tomography (CECT) scan of chest for the characterisation of SPN. Pre- and post-contrast CT of chest was performed on 16 slice spiral CT scanner.

It showed a heterogeneously enhancing lesion with spiculated margins seen in apico-posterior segment of left upper lobe. It measured 3.4x3.4x3.7 cm. It was infiltrating the visceral pleura (Figure 2).

Multiple, solid enhancing lymph nodes are seen at prevascular, left paratracheal, pre-tracheal, carinal and sub-carinal regions. Heart was enlarged in size with

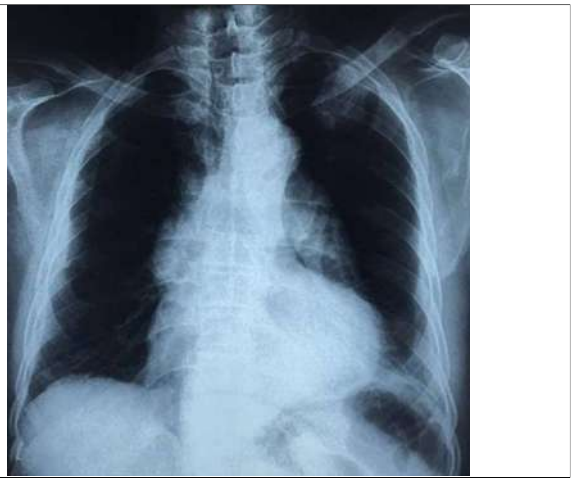

Figure 1: Chest X-ray showing solitary pulmonary nodule and aneurysmal dilatation of the descending thoracic aorta.

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cardiothoracic ratio of 14.2/23.5. Descending aorta was dilated and tortuous measuring 5.3 cm in diameter showing an intimal flap extending from D10 vertebra upto visualised L1 level with a thrombus within the aortic lumen (Figure 3).

The flap was extending into superior and inferior mesenteric arteries. Right renal artery was arising from false lumen and left renal artery from true lumen. Visualised sections of abdomen showed relatively reduced enhancement of right kidney compared to left kidney (Figure 4).

This patient denied any episode of chest or abdominal pain with normal bowel habits. Inspecting the complicated aortic dissection, the vascular surgery opinion was immediately taken; and he was planned for surgical repair.

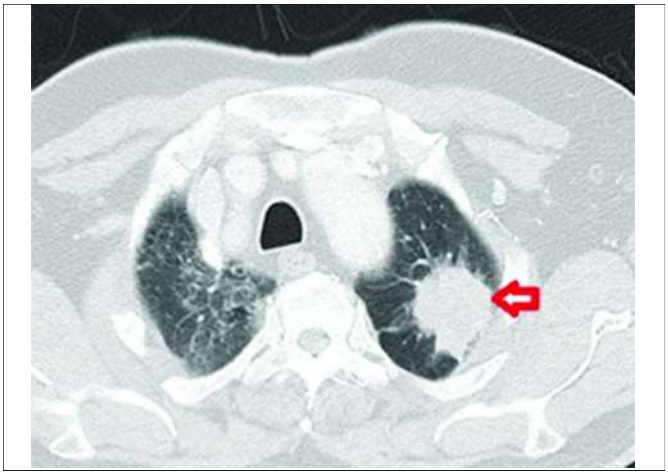

Figure 2: Axial CT section (lung window) showing solitary pulmonary nodule in left apico-posterior segment.

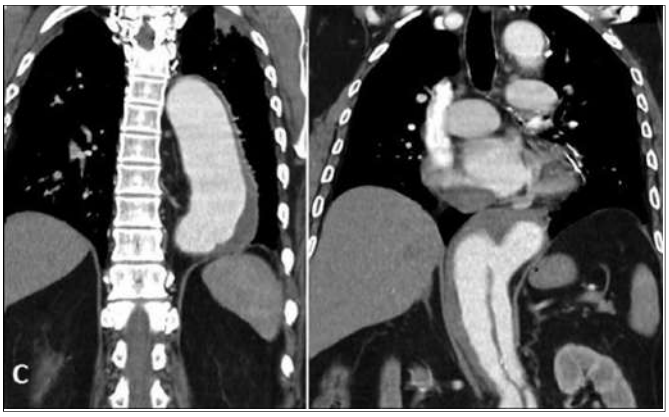

Figure 3: Contiguous coronal CT sections showing intramural haematoma and dissecting aortic aneurysm.

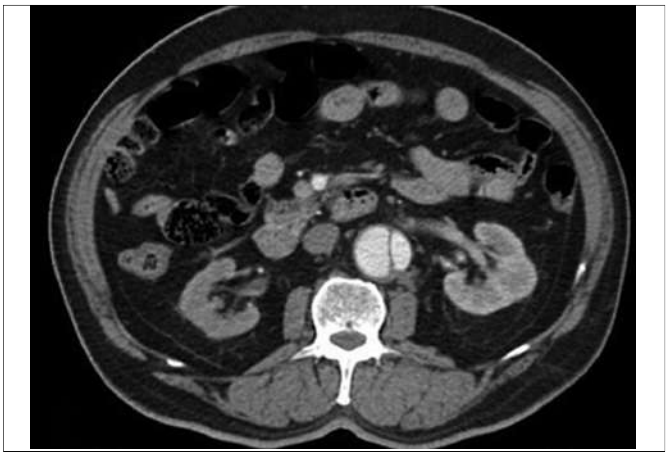

Figure 4: Axial contrast enhanced CT showing malperfusion of the right kidney.

DISCUSSION

The present case describes left upper lobe malignant lesion (T2, N3, Mx) with mediastinal lymph nodes. There was coexistent cardiomegaly with aortic intramural hematoma and dissecting aneurysm of the descending aorta, De Bakey III (Stanford B), extending into superior and inferior mesenteric arteries along with unilateral, right-sided renal ischemia.

The term acute aortic syndrome (AAS) is used to describe three closely related non-traumatic life-threatening aortic pathologies of the thoracic aorta. These include: aortic dissection, aortic intramural hematoma, and penetrating atherosclerotic ulcer.[3]

The International Registry of Acute Aortic Dissection (IRAD)[4] declared that out of all dissections, 38% were Stanford type B and only 63 patients (6.4%) had no chest pain.

In 2013, Bergmark *et al*. reported an acute, type B, aortic dissection in 43-year male, whose CT showed descending aortic dissection that initiated distal to the origin of the left subclavian artery with flap extension to bilateral iliac arteries and the left renal artery.[5] There was non-enhancement of the left kidney, representing ischemic change. He later underwent endovascular procedure for malperfusion syndrome.

The dissection of thoracic aorta can manifest in wide range of symptoms and requires a high index of suspicion as any delay in diagnosis may prove disastrous. An unusual presentation of thoracic aortic dissection in a 73-year man is described in a case report of Hado *et al*.[6] He was admitted to hospital with severe, left-sided, pleuritic chest pain. Spiral CT showed a false lumen in the ascending aorta. He underwent surgery but his condition worsened postoperatively because of intrathoracic hemorrhage and thus he developed cardiac tamponade; from which, resuscitation was not possible.

In 2008, Cohen *et al*. presented a case of a 54-year asymptomatic female, known case of hypertension and stage III chronic kidney disease, who presented to the OPD for pre-employment routine health screen.[7] She denied any episodes of chest pain, diaphoresis, syncope, altered mental status, focal neurologic deficit or symptoms of abdominal pain or bloody stools representing abdominal vasculature compromise. CT scan of the chest demonstrated an incidental aortic dissection extending from the aortic root along the right

lateral wall of the aortic arch. The robust literature search in local journals for aortic dissection revealed few case reports, all involving ascending aorta (type A).[8-10]

The present patient denied any history of chest or abdominal pain with normal bowel habits. After inspection of the complicated aortic dissection, the vascular surgery opinion was immediately taken; and he was planned for surgical repair.

Dissecting aortic aneurysm is a rare disease. It can present with tearing chest pain and acute hemodynamic compromise. Sometimes it may be asymptomatic as in this case. Early and accurate diagnosis and treatment are essential. There are few case reports reported on this topic internationally and locally in Pakistan. In the present case, a rare scenario of incidental dissecting aortic aneurysm is reported. The various clinical presentations and treatment options of aortic dissection are discussed. This case emphasises the importance of CT for diagnosing an asymptomatic aortic dissection.

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CASE REPORT

Vascular Resection and Reconstruction in Pancreatic Tumours

Sadaf Batool, Awais Amjad Malik, Hassaan Bari, Irfan ul Islam and Faisal Hanif

ABSTRACT

Option for borderline resectable pancreatic cancer is pancreaticoduodenectomy (PD) with vascular resection and reconstruction. We would like to share our experience of vascular reconstruction. First patient was a 51-year male with pancreatic head carcinoma, involving posterior wall of portal vein (PV) and replacing right hepatic artery (RHA). Along with PD, he underwent PV and RHA resection and reconstruction. Second case was a 33-year female who had distal pancreatic cyst and PV-splenic vein junction involved by tumor. Distal pancreatectomy+splenectomy and PV primary resection-reconstruction was done. Third case was a 72-year male with pancreatic neck adenocarcinoma involving PV-SMV junction. Subtotal pancreatecomy+splenectomy was done along with PV-reconstruction via splenic vein patch graft. Fourth case was a 77-year male with cystic pancreatic head mass involving PV. PD with resection and reconstruction of portal vein was done. Fifth case was a 35-year female with peri-ampullary tumor replacing RHA, coursing through the pancreatic parenchyma. So RHA was resected and reconstructed in an end-to-end fashion. Vascular resection-reconstruction can be done in borderline pancreatic cancer patients, and a considerable survival benefit can be achieved.

Key Words: *Pancreaticoduodenectomy. Pancreatic cancer. Vascular resection. Portal vein.*

INTRODUCTION

Surgery remains the mainstay of treatment for patients with pancreatic cancer as it is the only hope for long-term survival in such patients.[1] Main objective is to achieve resection with microscopic clear margins.[1] However, some patients present with involvement of portal vein (PV) and hepatic arteries and are labelled as borderline resectable.[1] The only surgical option in such patients, to achieve tumor-free margin, is vascular resection with reconstruction.[2] Pancreaticoduodenectomy with vascular reconstruction (PDVR) has been reported in various case series. It has shown to be safe and feasible with similar long-term outcomes as long as one achieves a negative resection margin (R0).[2] The first report of PDVR was by Moore and colleagues, who, in 1951, performed the first superior mesenteric vein (SMV) resection and reconstruction, followed by Asada and colleagues from Japan in 1963.[3,4] In 2004, Tseng and colleagues from the MD Anderson Center, found no survival difference in patients undergoing PD and PDVR.[5] Similarly, Yekebas and colleagues, in 2008, found similar postoperative morbidity and mortality rates between PD and PDVR.[6]

In 2009, the American Hepato-Pancreatico-Biliary Association and Society of Surgical Oncology (AHPBA/SSO) formulated a consensus statement. They concluded that PD with vein resection and reconstruction is the standard of practice for pancreatic adenocarcinomas locally involving the SMV-PV confluence, provided that adequate inflow and outflow veins are present, that the tumor does not involve the superior mesenteric artery (SMA) or hepatic artery (HA), and that an R0/R1 resection is reasonably expected. The consensus statement went on to say that patients with non-metastatic adeno-carcinomas should be evaluated and resected at institutions capable of, and experienced in, resection and reconstruction of major mesenteric veins.[7]

We would like to share our experience at Shaukat Khanum Memorial Cancer Hospital of vascular reconstructions for pancreatic cancers. In a period of two years, we had five patients with pancreatic cancer who had either borderline resectability on a preoperative CT scan or unexpected PV involvement was observed intra-operatively due to disease progression. PD was performed in three patients; whereas rest of the two patients had distal pancreatectomy, with vascular reconstruction. A brief discussion on each case is done and presented herewith.

CASE REPORT

Case 1: First case was a 51-year male, known hyper-tensive, presenting with jaundice for one month. CT revealed pancreatic head mass with involvement of peri-portal nodes. Endoscopic ultrasound (EUS) with biopsy showed pancreatic head adenocarcinoma, T3, with involvement of regional nodes. During surgery, it was observed that the tumor was involving posterior wall of PV and right hepatic artery was originating from SMA. Part of both the vessels involved by tumor was resected and reconstructed. PV was repaired end-to-end with prolene 5/0 and RHA was repaired end-to-end with prolene 7/0. Total operative time was 11.45 hours with

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blood loss of approximately 700 mls. After 24 hours postoperative ICU stay, patient was shifted to floor. There was no immediate postoperative complication and he was sent home after one week of surgery. He made initial recovery and completed his chemotherapy. He developed disease relapse in the form of pulmonary metastasis at 13th month and passed away at 15th month after surgery.

Case 2: A 33-year female presented with an epigastric mass for one month. CT scan showed cystic lesion in the body of pancreas with involvement of PV-splenic vein junction and splenic vein thrombosis. EUS with fine needle arpiration (FNA) was done and it was diagnosed as pancreatic body serous cystadenoma. Intra-operatively, a large tumor was observed densely adherent to surrounding structures, including transverse meso-colon, stomach and lesser sac. Distal pancreatectomy with PV resection and reconstruction and splenectomy was performed. PV was repaired in end-to-end fashion with prolene 6/0. Duration of surgery was 4 hours with blood loss of 1200 ml. Postoperatively, Doppler showed normal PV flow. Postoperative course was uneventful and patient went home after 5 days. Histopathology report showed mucinous cystic carcinoma with clear margins. She is doing well 2 years after surgery.

Case 3: A 72-year male, known hypertensive, presented with abdominal pain and weight loss for the last 3 months. CT abdomen showed pancreatic neck mass without any vascular involvement. EUS and staging CT was done which showed T3, N0, M0 pancreatic neck adenocarinoma. Intraoperatively, tumor showed disease progression, involving PV and splenic vein junction. Subtotal pancreatectomy was done with PV/SMV junction resection. His splenic vein was retrieved, split opened and used as a patch graft for PV reconstruction (Figure 1). Operative time was 4 hours and blood loss was 200 ml. Postoperatively, he was discharged home after eight days without any complication. He was thought to be too frail to tolerate chemotherapy and developed liver metastasis, 12 months after surgery. He was lost to follow-up afterwards.

Case 4: Fourth case was a 77-year male who presented with epigastric pain and weight loss for 2 months. Contrast-enhanced CT abdomen revealed cystic mass within pancreatic head involving PV. CT also showed a nodal mass around SMA (Figure 2). EUS and staging CT showed T3, N1, M0 pancreatic head tumor. During the surgery, it was found that tumor was involving a segment of PV with encasement of posterior and superior walls and a nodal mass around SMA. Whipple procedure was done with PV resection and end-to-end reconstruction with prolene 6/0. Careful dissection of lymph node mass around SMA was done. Surgery lasted for 12 hours with blood loss of 1500 ml. Postoperatively, patient was kept in ICU for 3 days as he developed pancreatitis with

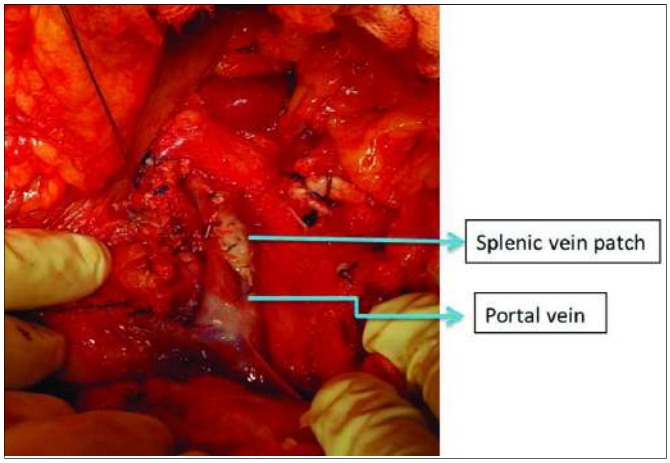

Figure 1: Intraoperative picture of portal vein reconstruction with splenic vein graft.

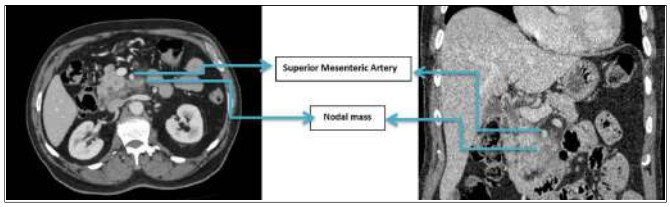

Figure 2: CT abdomen showing portal vein encasement in tumor of head of pancreas in axial section and coronal section.

acute kidney injury. He was kept on ventilator for first postoperative day and was shifted to floor after 2 days. He had high drain output, which was milky white, and drain fluid triglyceride levels were raised. Diagnosis of chyle leak was made, which was successfully managed conservatively with total parental nutrition for two weeks. His chemotherapy treatment could not be completed due to side effects. He died with disease recurrence at 12th month.

Case 5: Last case was a 35-year female without any known comorbids, who presented with pain in abdomen, jaundice and unintentional weight loss for 3 months. ERCP was done and a peri-ampullary growth was seen. Biopsy showed it to be adenocarcinoma. Staging CT scan showed a resectable peri-ampullary tumor with no metastasis. The tumor encased RHA, which was arising from SMA; whereas left hepatic artery was arising from celiac artery and giving gastroduodenal branch. Intra-operatively, the replaced RHA was coursing through the pancreatic parenchyma. PD was done with resection and reconstruction of aberrant RHA with prolene 6/0 in end-to-end fashion. Postoperative course was uneventful. Postoperative CT showed patent repaired RHA and no collection. Histopathology showed adenocarcinoma with clear margins. She was followed for a period of 40 months and was disease-free till last follow-up.

DISCUSSION

Locally advanced pancreatic cancers with PV involvement is no longer a contraindication to surgery. PD with PV

reconstruction, although still not a common practice, but has secured its place in the surgical management of patients with borderline resectable tumor of the head of the pancreas. It has been suggested that PDVR might be associated with a higher complication rate when compared with PD.[8] The median overall survival duration for patients without surgery is less than 12 months.[9] The median overall survival duration for the patients who underwent pancreatectomy with clear margins was 27.8 months.[9] The variation in morbidity rates with PDVR is substantial, varying from 30% to 55%.[10] We have presented our experience of 5 cases with borderline resectable pancreatic cancer that underwent PV and/or replaced hepatic artery resection and reconstruction. There was no in-hospital mortality. Most of our patients were followed up till one year (ranging from 12 to 40 months). Two mortalities were recorded, at 12 and 15 months. Recurrence or metastatic disease was noticed in three patients including liver, pulmonary and peritoneal metastasis. Maximum disease-free survival was 40 months (ranging from 12 - 40 months). It is likely that vascular involvement is an independent predictor of distant metastasis despite clear margins. However, a study with large sample size is required to look into it, more precisely.

Vascular reconstruction with PD does add morbidity and complexity to an already lengthy operation. However, this aggressive surgical approach with vascular resections and reconstructions are the only hope for longer survival for borderline pancreatic tumor patients. With proper preoperative assessment and patient selection, tumor resection and PV reconstruction with negative margins can be achieved.

This case series suggest that addition of vascular resection to pancreaticoduodenectomy for pancreatic adenocarcinoma is feasible in a specialised setup. Although it is associated with increased risk of postoperative morbidity; but the survival benefit this aggressive and curative approach provides, is considerably much more than doing nothing for borderline pancreatic cancers.

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CASE REPORT

Classical Homocystinuria in a Juvenile Patient

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ABSTRACT

Classical homocystinuria, also known as cystathionine beta synthase deficiency, is a rare disorder of methionine metabolism, leading to an abnormal accumulation of homocysteine and its metabolites in blood and urine. A young child with homocystinuria is discussed, who presented with behavioral abnormalities, involuntary movement, mental retardation, and decreased vision since birth. The diagnosis of homocystinuria was not made at initial presentation. Subtle phenotypic features with developmental delay and MRI brain finding of bilateral medially dislocated lens, eventually provided the first indication at five years of age. Laboratory screening with plasma amino acid profile by ion exchange chromatography (IEC) showed elevated homocystine and methionine, and low cystine in plasma in the absence of vitamin B12, and folate deficiency; giving the diagnosis of classical homocysteinuria.

Key Words: *Homocystinuria. Hypermethioninemia. Cystathionine-β synthase (CBS) deficiency. Inherited metabolic disorder (IMD).*

INTRODUCTION

Homocystinuria is an autosomal recessive inherited defect of methionine metabolism, which leads to an abnormal accumulation of homocysteine and its metabolites (homocystine, homocysteine-cysteine complex) in blood and urine. There may be a defect in the trans-sulfuration pathway due to deficiency of cystathionine-β synthase (CBS) -homocystinuria I) or methylation pathway (homocystinuria II and III) of methionine metabolism.[1] These biochemical disturbances have both genetic and non-genetic causes. Reported incidence of homocystinuria varies between 1 in 50,000 to 1 in 200,000.[2] Data suggest that starting at around early infancy to teenage, these patients have an increasing likelihood of suffering from a thromboembolic event.[3] Clinical variability in the phenotypic features of homocystinuria is well recognised; as a result, the condition may be overlooked due to similarity in clinical features of vitamin B12 and folate deficiencies.[4] After folic acid and vitamin B12 deficiency exclusion, initial diagnosis is best achieved by quantitative plasma amino acid analysis of plasma. MRI and CT findings may show both large-vessel or lacunar strokes, potentially in any vascular distribution.[5] Correcting nutritional inadequacy of folic acid, vitamin B12, B6 and betaine lowers homocysteine levels. A low methionine diet with betaine supplementation are also useful.[6]

CASE REPORT

A 5-year boy, resident of Kotli, Azad Kashmir, was referred to the Pediatric and Metabolic Department of Armed Forced Institute of Pathology (AFIP), Rawalpindi for amino acid analysis. He was admitted for evaluation of decreased vision since birth and impulsivity, hyperactivity and involuntary movements of right leg of one-month duration. There was no history of seizures or loss of consciousness. He was born at 39 weeks' gestation through spontaneous vertex delivery with a birth weight of 3.8 kg. He was a child of non-consanguineous marriage with two siblings. There was death of the eldest brother at the age of nine years due to unknown cause and this sibling has had decreased vision since birth. This patient had delayed developmental milestones, particularly speech deficits, and could only utter a few words. General physical examination showed a hyperactive and irritable child who was 110cm tall (between 50th and 75th percentile) and weighed 20 kgs (75th percentile). Facial features showed mild dysmorphism. His scalp hair was thin, brittle and

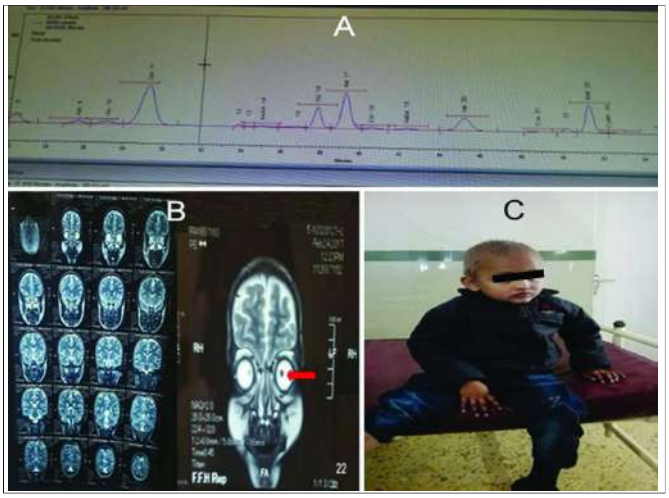

Figure 1: (C) Frontal view of patient showing relative nonspecific facial features and thin brittle, discolored hairs. (A) Plasma aminoacid profile chromatogram showing markedly increased peak of methionine and low peak of cysteine with rest of aminoacids had normal chromatogram peaks. (B) MRI showed bilateral medially dislocated lens with no abnormal enhancing area in brain.

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lusterless (Figure 1). An ophthalmologic examination showed a high myopic refractive error and bilateral lens subluxation. Neurological examination revealed normal findings. The combination of ocular findings and phenotypic features suggested homocystinuria as the underlying metabolic cause for his developmental delay. MRI brain showed bilateral medially dislocated lens.

The biochemical findings supporting the diagnosis: (1) Plasma amino acids analysis in lithium heparin tube by ion exchange chromatography (IEC), showed elevated methionine of 182 μmol/L (normal 3-43) and a low cysteine value of 4.7 μmol/L (normal 23 - 68) and elevated plasma homocysteine levels which was done by turbidimetric inhibition immuno assay (TINIA)-225 μmol/L (5-15 μmol/L-Desirable, 15-30 μmol/L- Moderate, >30 μmol/L- High Risk). (2) Blood screening tests showed raised plasma ammonia and serum alanine aminotransferase (ALT), with normal plasma lactate and normal renal function tests. (3) Urine for qualitative metabolic screening, ketone bodies and reducing substances was unremarkable. (4) Serum folate and serum vitamin B12 levels were normal.

Based on above findings, the case was labelled as that of classical homocystinuria. As enzyme assays were not available, so exact enzyme deficit could not be confirmed. The patient was started on pyridoxine, 500 mg, once a day, folic acid, 5 mg once a day, and a low methionine diet. Dietary compliance till then has been poor. The patient showed no biochemical response to pyridoxine administration. Since the patient did not respond to pyridoxine, the parents were advised to continue him on a low methionine / high cystine diet. He was followed up on quarterly basis for checking any improvement in his biochemical profile and mental activity with diet modification.

DISCUSSION

Homocystinuria, mostly due to cystathionine-β synthase (CBS) deficiency is an intoxication group inherited metabotic disorder (IMD). Our case was typical in the sense that it had abnormalities of three out of the four organ systems involved in CBS deficiency, namely, ocular (decreased vision and subluxation of lens), skeletal (high arched palate, long and slender fingers, joint hypermobility), and CNS (impulsivity, hyperactivity, speech deficit). Ocular presentation is a characteristic feature of this disease; and was the presenting feature in our patient. Thromboembolic complications were not seen in our patient, probably due to the younger age at presentation.[1,3,4] However, death of his sibling at nine years of age and consequent to cerebrovascular accident does merit a strict follow-up in this patient with dietary modifications to alter the progress of disease. This also indicates that genetics has a strong role to play in this disorder. Studies have revealed a strong correlation of phenotypes and complications among siblings.[1,5]

Deficiency of CBS leads to tissue accumulation of methionine, and homocysteine with low levels of cysteine. These laboratory findings were seen in the patient with marked elevation of both homocysteine as well as methionine, much higher than similar case reports in the past.[4,5] Immediate processing of the sample received in our department in order to prevent loss of disulfide amino acids as they have a tendency to bind to proteins, could have attributed to the well preserved higher levels in this patient. We ruled out secondary causes of hyper-homocystinemia in our patient by the normal renal function tests, and normal folate and vitamin B12 levels. In our case, MRI brain changes were consistent with findings in literature.[3]

Enzymatic confirmation of the diagnosis of classical homocystinuria should ideally be done by measurement of CBS enzyme activity in cultured skin fibroblasts. It was, however, not carried out in this patient due to non-availability of the facility in our set-up.

The aim of treatment is to reduce plasma total homocysteine levels as close to normal as possible while maintaining normal growth rate along with pyridoxine and folic acids supplementation, in order to reduce thromboembolic events and neurological abnormalities.

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Utility of Routine Gall Bladder Histopathology after Living Donor Hepatectomy in Liver Transplantation

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ABSTRACT

Intraoperative cholangiogram with cholecystectomy is a routinely performed procedure in living donor liver transplantation (LDLT).The objective of this study was to determine the frequency of gall bladder pathology in healthy living donors and whether routine histopathology can be omitted. This was a retrospective review of 366 donors who underwent donor hepatectomy between 2012 and 2016. Primary outcome of interest was frequency of abnormal histopathology findings in removed gall bladder specimen; and if their distribution was different with respect to gender, age and BMI. Male to female ratio was 2.1:1. Median age was 26 (18-50) years. Median BMI was 23.9 (15.7-35) Kg/m^2. The most common finding was chronic cholecystitis in 189 (51.6%). Gall bladder pathology was more frequently seen in donors with BMI >25 Kg/m^2, i.e. 69.3 % versus 30.7% (p<0.001). Due to high frequency of abnormal findings, gall bladder should be sent routinely for histopathology in healthy liver donors after cholecystectomy.

Key Words: *Cholecystectomy. Healthy donor. Chronic cholecystitis. Histopathology. Gall bladder pathology.*

In the West, cadaveric organ donation remains the primary source for liver transplantation. Many countries in Asia, including Pakistan, have certain limitations which prohibit retrieval of organs from deceased donors for transplantation.[1] Living donor liver transplantation has been the primary source of organ retrieval in these regions. Cholecystectomy is routinely performed in living donor hepatectomy and the specimen is sent for histopathology.

The objective of this study was to determine frequency of various gall bladder pathologies in healthy living donors; and if routine histopathology can be omitted.

This was a retrospective review of donors who underwent donor hepatectomy between April 2012 and October 2016. A total of 366 voluntary donor hepatectomies were performed during this period. Donors who had a previous cholecystectomy (N=3) or did not undergo gall bladder removal (N=4, since they underwent left lateral grafts not requiring cholecystectomy) were excluded from the study.

Donors were 18-50 years of age, and blood group compatible and related to the recipient. They underwent extensive preoperative workup to determine their suitability for voluntary liver donation. In addition, a dynamic liver CT scan and MRI was performed to look for previously unknown abnormalities, delineate vascular and biliary anatomy of the liver; and to determine graft size and volume. All transplants were performed after approval from the Hospital Committee and the Human Organs Transplantation Authority (HOTA), Pakistan. A cholecystectomy was performed as part of intraoperative cholangiography. Patients under-went retrograde cholecystectomy and specimen was sent for histopathology. Pathology review was performed by consultant pathologists experienced in performing hepatobiliary histopathology review.

For the purpose of this study, impact of demographic variables, histopathology findings, age and BMI (reported as median and interquartile range) was determined on distribution of abnormal findings in donors. Data for gender was reported as frequencies and percentages. For categorical variables, Chi-square test was used. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 20. The hospital Ethics Committee granted ethical approval for this study.

A total of 366 donors were included in the study. There were 251 (68.5%) male donors. Median age was 26 (IQR=18-50) years. Median BMI was 23.9 (IQR= 15.7-35) kg/m^2. Most donors donated a right lobe graft (n=353, 96.4%) and were closely related to the recipient. The relationship of donor to recipient was son to father in 102 (27.9%), and nephew to uncle in 57 (15.6%) donors. The most common finding was chronic cholecystitis in 189 (51.6%), followed by a normal gall bladder in 157 (42.8%) donors. There were 10 (2.7%) donors with congestion, 5 (1.3%) with cholesterolosis, 2 (0.5%) with acute on chronic cholecystitis, 2 (0.5%) with gangrenous GB and 1 (0.3%) with hemangioma of gall bladder. Table I demonstrates the impact of donor

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Table I: Distribution of GB findings in donors with respect to gender, BMI and age groups.

	Normal GB (N=157)		Abnormal GB (N=209)		p-value
	Number	Percent	Number	Percent	
Gender					
Male (N=251)	113	45	138	55	0.2
Female (N=115)	44	38.2	71	61.8	
BMI					
<25 (N=223)	113	50.6	110	49.4	<0.0001
>25 (N=143)	44	30.7	99	69.3	
Age group					
<40 (N=333)	146	43.8	187	56.2	0.2
>40 (N=33)	11	33.3	22	66.7	

gender, age and BMI on histopathology findings in GB specimen. Distribution of histopathology findings was significantly different in donors with respect to BMI. The percentage of donors with a normal or abnormal GB on histopathology were comparable as 113/223 versus 110/223, (50.6% versus 49.4%) in BMI <25 group; however 99/143 (69.3%) donors in BMI >25 group had abnormal histopathology findings (p<0.001).

The current study demonstrates high frequency of GB pathology in healthy Pakistani individuals, selected for voluntary liver donation. A high percentage of donors had cholecystitis that was not related to gallstone disease. There was no significant association between age or gender and the frequency of gall bladder pathology.

Well established risk factors for GB cancer include advanced age, obesity, chronic gall bladder inflammation; and South American, Indian or Pakistani origin.[2] Siddiqui and colleagues reviewed histopathology reports in 220 Pakistani patients who underwent cholecystectomy and found adenocarcinoma in 2.8% patients. More than 50% of patients in this study were <40 years of age. They also highlighted a 'not so rare' practice of discarding cholecystectomy specimens, if visual inspection was normal. They concluded that routine histopathology should be performed in all removed gall bladders.[3]

Studies performed on GB histopathology are usually on symptomatic patients with complaints of acute or chronic cholecystitis. Literature on histopathology findings in healthy individuals does not exist as there is no reason to perform cholecystectomy, otherwise. Living donors represent a unique group of individuals who are healthy, fit and symptom-free, but undergo cholecystectomy purely on merits of their surgical procedure. Recently, Akbulut and colleagues performed a review on similar topic. Frequency of abnormal findings in their study was much lower compared to current study. Overall, 25% patients had abnormal histopathology.[4] This might be due to underlying demographic differences in the two studied populations.

There arise few questions: (1) Since chronic cholecystitis leads to increased GB cancer risk, is there a need for screening programme in our population? (2) Can one exclude routine GB histopathology in donors in an attempt to reduce pathologist's workload?

To answer these questions, more quantitative data is needed. Given the present data, routine histopathology should not be omitted. It has been shown that even with frequency of incidental GB cancer on removed specimen as low as 0.25%, the cost per life year gained favours for routine histopathology.[5] Limitations of the current study include lack of classification, based on degree of chronic cholecystitis.

The current study demonstrates high frequency of GB pathology in healthy Pakistani population and indicates prevalence of chronic cholecystitis in high BMI individuals. GB histopathology should remain a routine in living donor liver transplantation; and a routine preoperative ultrasound (US) may be helpful to provide valuable information in donors. Since Pakistan represents a high prevalence zone for GB cancer, there is a need to develop screening guidelines. Caution should be practised in routine practice of discarding gall bladder specimens in patients with symptomatic gallstones, based on grossly normal appearance.

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Training Pediatric Mechanical Ventilation to Front Line Pediatric Physicians

Mechanical ventilation (MV) is one of the defining interventions of critical care medicine helping save millions of patients' lives.[1] Providing pediatric critical care in Pakistan is a unique challenge because of limited, less prioritised resources and lack of training.[2] Because of few centres having trained pediatric intensive care unit (PICU) physicians, MV is being managed by residents/nurses/non-ICU physicians, while MV is not included in their curriculum.[3] Without proper training, this life-saving machine can be a weapon of "mass destruction".[4]

Keeping need-demand gap in mind, we designed a half-day course on MV with the aim to train frontline pediatricians on use of MV at 10 tertiary care academic hospitals in two cities of Pakistan; all of these centres had postgraduate pediatric residency programme and mechanical ventilators. Target audience was pediatric trainees, nurses and consultants who were working in PICU, and were actively involved in providing care to children requiring MV. This 4-hour course consisted of didactic lectures covering anatomic and physiologic airways differences in infants and children, concepts and principles of MV, initiation, monitoring, trouble-shooting and liberation from MV in the first half; followed by small-group (4-5 persons) hands-on training on MV machine with artificial lung with common case scenarios of acute respiratory insufficiency in the second half. Each course had a written pre- and post-test covering aspects discussed during the course.

A total of 311 participants were trained in 17 courses from July 2013 to December 2016; including 234 pediatric trainees, 26 consultants, and 31 PICU nurses. The mean (±SD) percentage of scores in pre- and post-test were 50.63% ±27.22 and 62.12% ±23.19, respectively; with an increase in mean percentage of scores in pre- and post-test of 11.49% ($p<0.001$). Median of the overall evaluation of the course on a 5-point Likert Scale was 4; the course was excellent. Highest evaluations were given to 'acquired new knowledge', 'time management' and 'objectives of activity were defined'.

Focused educational intervention, like this, increased the knowledge which was unsatisfactory in the pre-test. The translation of this knowledge into practice has the potential of improving clinical outcomes of sick children and saving many preventable deaths.

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Giant Primary Enterolith: An Offbeat Clinical Presentation and a Word of Caution

Sir,

Enteroliths, the intra-luminal intestinal concretions, are known to have varied clinical presentations.[1-3] We describe a case wherein primary ileal enterolith precisely mimicked giant vesicolith and eventually led to per-operative bafflement. The stark disparity between our algorithmic thought-spiral and the actual surgical finding, made it rather educational. To our knowledge, such case is yet to be reported.

A 31-year lady presented with typical lower urinary tract symptoms (dysuria, frequency) and recurrent urinary tract infection (UTI) for over three years. She also experienced on-and-off, dull-aching, supra-pubic pain without urinary retention or hematuria. Barring mild hypo-gastric tenderness, her examination and hematological/ renal parameters were normal. Yet, urine demonstrated 12 pus-cells and 8 red-cells/HPF. Abdominal radiogram illustrated a large radio-opacity in pelvis (Figure 1). Ultra-sonography confirmed a 5 x 4 cm urinary bladder (UB)-stone without hydroureter/nephrosis. Subsequently, she was planned for standard open vesicolithotomy. However, vesicotomy did not yield any stone. Detailed digital exploration supplemented by C-arm examination summarily failed as well. Suspecting uncommon erosion, peritoneum was opened to discover multiple strictures in short ileal segment (Figures 2A and B); the so-called "vesicolith" was actually an enterolith entrapped between these strictures (Figures 2C and D). Rest of abdominal viscera, including the gallbladder, was normal. Accordingly, limited ileal resection-anastomosis, followed by UB repair, was performed by standard surgical techniques. She recovered well and was discharged on day-7. Histopathology, nonetheless, showed non-specific enteritis.

This case has certain unique features – strong diagnostic resemblance of enterolith with vesicolith until surgery table – it could plausibly be due to repeated extrinsic compression and resultant local irritation of the UB-wall by the enterolith. Despite near-total luminal compromise, it lacked features of mechanical bowel obstruction, when >2 cm calculus would readily do so.[1,2] This could be attributed to its "ball-valve" effect at the partially incompetent stricture. It was a female patient without any bladder outlet obstruction, when males are the usual reported sufferers.[4] Flawed preoperative diagnosis prevented further investigations like computed tomo-graphy (CT) or cystoscopy. In that context, though CT has higher sensitivity, ultra-sonography seems preferred choice as it circumvents cumulative radiation exposure without affecting the diagnoses.[5] As a result, it was neither possible to prognosticate the disease nor obtain pertinent preoperative informed consents from the patient's kin.

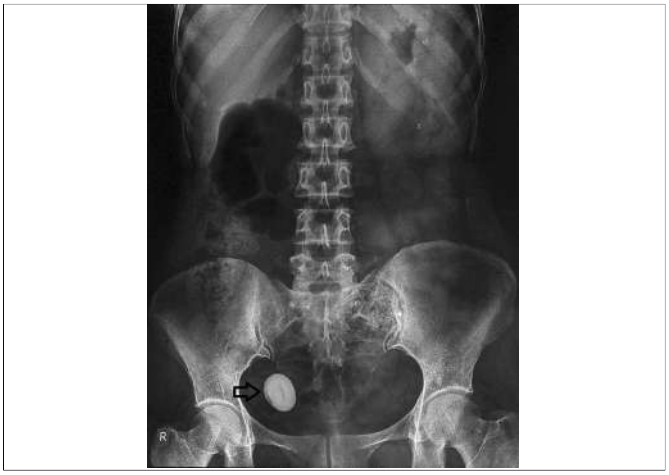

Figure 1: Erect abdominal X-ray depicting a large radio-opacity in the region of the urinary bladder (arrow). Note absence of nephro/ureterolithiasis, air-fluid levels or pneumobilia, thus ruling out gallstone ileus. Also note the characteristic lamellar morphology with central lucency of the calculus that substantiated our flawed preoperative diagnosis of giant vesicolithiasis.

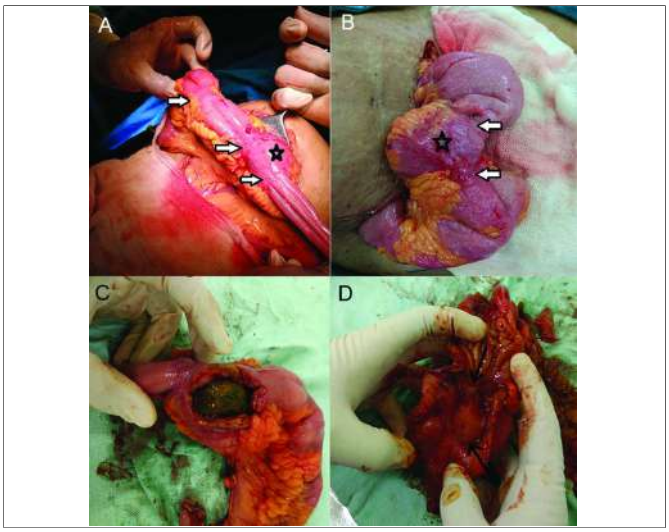

Figure 2: (A, B) Exploratory laparotomy revealing multiple ileal strictures (white arrows) with trapped enterolith (star). Note absence of intestinal dilatation ruling out any acute obstructive element, thus facilitating unhindered small bowel delivery. Further, note the thickened and erythematous enteral wall deferring stricture-grading by digital palpation; also, mesenteric fat-wrapping in the vicinity of strictures suggesting Crohn's enteritis. **(C)** Cut-open specimen with a giant oblong calculus retained between the ileal strictures. **(D)** Specimen showing fibrotic strictures (black arrows) without any ulcero-proliferative growth.

In conclusion, enterolithiasis should always be kept in mind while dealing with vesicolithiasis; also prudently maintain a low threshold to tailor to CT and/or cystoscopy for avoiding "on-table" surprises and resulting potential litigations.

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Sexual Dysfunction and Depression in Pregnancy

Sir,

Female sexual dysfunction (FSD) is a highly prevalent health problem that affects approximately 40-50% of the women.[1] FSD occurs as a part of various medical conditions like cardiovascular disease, diabetes mellitus, psoriasis, depression and anxiety.[2] Pregnancy is a physiological phase in the life of a woman; but for many women, this is the time of fear, stress, confusion and even depression. All the biological functions of the body are altered to some extent during the pregnancy including the appetite, sleep and sexual function.[3] Some of the factors that may affect sexual function during pregnancy have been reported as weight gain, nausea, fatigue, breast tenderness, and fears regarding coarse of pregnancy and fetal health. Sexual dysfunction, if persists for a long period, can lead to emotional distress and compromised quality of life, which may not be desirable for good maternal and fetal outcome. Depression and other mental health issues are common during the pregnancy. Sexual dysfunction, depression and anxiety are interlinked during pre-natal and post-natal period, so screening of sexual dysfunction may be useful in early detection and treatment of these disorders.[4,5] This survey was planned to look for depression and sexual dysfunction among pregnant women of AJK in order to estimate the prevalence of these issues and their relationship with each other to make their early detection and treatment possible.

We studied 161 pregnant women reporting for the ante-natal checkup at a tertiary care hospital in Azad Jammu and Kashmir (AJK). Sexual function was assessed using the female sexual function index (FSFI). Depression was assessed by using the Patient Health Questionnaire-2 (PHQ-2). Relationship of age, gestation, parity, depression, planned or unplanned pregnancy, duration of marriage, previous loss or complication, occupation, worry about future, education, level of family income, and tobacco smoking was assessed with the sexual dysfunction. About one fifth (19.9%) of the women had normal sexual function, while 80.1% had sexual dysfunction. After applying logistic regression, it was found that parity, tobacco smoking, worry about future, previous loss or complication, duration of marriage, and depression had significant association with the sexual dysfunction.

This study showed a high prevalence of sexual dysfunction among pregnant women in AJK. Strong relationship of sexual dysfunction with depression has also been established. Previous studies have also concluded that sexual dysfunction and depression can co-exist in pregnancy and a positive feedback cycle sometimes develop between the two, which becomes very annoying for the patient and a challenge for the healthcare physicians.[4,5] Questioning about sexual functionality and depression are normally not a part of routine examination in obstetric clinics of our country. Keeping in mind the results of this study, asking about sexual dysfunction, and screening the depressive illness should be a part of routine obstetric evaluation so that early intervention could be done by using a multi-disciplinary approach to treat these problems effectively.

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Emphysematous Cystitis in a Non-Diabetic Male

Sir,

Emphysematous cystitis (EC) is a rare urinary tract infection that is caused by gas-producing bacteria colonising the urinary bladder. Diabetic and female patients are more prone to develop EC. Most often its diagnosis is made incidentally during imaging investigations of the patient with symptoms of cystitis. Initial treatment consists of giving intravenous antibiotics. In severe cases, where the kidney is also involved, nephrectomy can be performed for the cure.[1] In untreated cases, bladder rupture and septicemia can also occur as one of the worst outcomes. We present a case in which a male was suffering from EC.

A 55-year male presented to Emergency Department with complains of fever, flank pain, and burning micturition. The vital sign on presentation read as blood pressure 110/80 mmHg, heart rate 103 bpm, respiratory rate 22 breaths per minute, temperature 101°F, and oxygen saturation 96% at room air. He had pain in abdomen, nausea, and decreased appetite. He had no comorbid condition such as diabetes mellitus. The patient had a past medical history of carcinoma colon; and for that, left hemicolectomy was done. The patient underwent a non-contrast CT to see if there was any stone in kidneys or urinary tract. It showed a 20 mm lower pole stone in right kidney. There were air pockets within the bladder wall (Figure 1). As the patient had previous history of left hemicolectomy for colon cancer, so presence of any enterovesical fistula was ruled out by doing the urine routine examination, which was free from debris or fecaluria, which is pathognomonic of a fistula. Clinically enterovesical fistulae may be described as Gouverneur syndrome, namely, suprapubic pain, frequency, dysuria, and tenesmus. In this patient, there was no complaint of tenesmus. Other signs of fistula include abnormal urinalysis findings, malodorous urine, pneumaturia, and debris in the urine. Patients may describe passing of vegetable matter in the urine. The flow through the fistula predominantly occurs from the bowel to the bladder. Patients very rarely pass urine from the rectum. This patient did not give any such history. Barium enema study was also done to see if contrast could be seen leaking into the bladder, on images. It was found that there was no contrast leakage into bladder so enterovesical fistula was ruled out completely.

According to the culture and sensitivity report of urine, the patient was treated with Pip-Tazobactam 4.5g three times a day for 10 days and discharged in stable medical condition. He was then advised to be followed up for renal stone treatment.

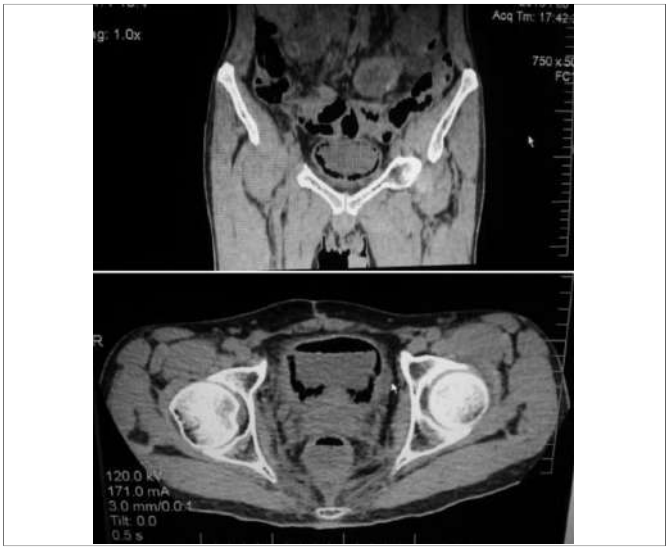

Figure 1: Incidental finding on the CT of pneumaturia, suggestive of EC.

Pyelonephritis, uncomplicated cystitis, and emphysematous cystitis can be difficult to differentiate clinically, based on symptoms only, as each of them can present with abdominal pain, dysuria, burning micturition, and hematuria.[1,2] Pneumaturia may be present in patients with EC, and can help the clinician about suspicion of EC, but it should be kept in mind that pneumaturia may also occur in emphysematous pyelonephritis. EC is found more in female patients over the age of 60 years, with 60-70% of the cases occurring among diabetic cases.[1] The most sensitive tool to make diagnosis of EC is the presence of air pockets surrounding the urinary bladder on CT.[2] Urinalysis done in such patients is nonspecific as it closely resembles picture of pyelonephritis with the presence of white blood cells, red blood cells, and many bacteria.[2] If it is not treated in time, it can lead to bacteremia in 50% of cases.[1,3] Medical therapy with antibiotics is the most common and effective treatment.[5]

One of the theories of pathogenesis propose that gas formation might occur when bacteria such as *E. coli* ferment the glucose present in the urine. This might explain the higher rate of infection that occurs in the diabetic patients. While in non-diabetic patients, local inflammation and impaired circulation have been thought as the possible mechanism of pathogenesis.[5] One of the complications of EC is emphysematous pyelonephritis, which presents in a way similar to acute pyelonephritis, with symptoms of abdominal pain, flank pain, fever, chills, nausea, vomiting, and leukocytosis.[3] It is typically diagnosed with the help of abdominal CT

scan. Its treatment includes use of intravenous antibiotics and open drainage or, in severe cases, emergency nephrectomy.[2,3] This patient's presentation and laboratory investigation reports fit the classic description and findings of EC.

It is important to note here that EC can occur even in non-diabetic male, which is a rare entity.

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Osteoid Osteoma of Jaw in a 54-Year Male

Sir,

Osteoid osteoma of jaw is a unique and uncommon tumor characterised clinically by continuous or intermittent pain which frequently becomes worse at night and histologically comprised of osteoid and trabeculae of newly formed bone with highly vascularised stroma.[1] Only 20 cases of osteoid osteomas have been reported in the jaw bones so far.[1-3] Majority of jaw osteoid osteomas are reported in second and third decade of life. According to Jaffe, curious pain seen in osteoid osteoma is attributable to the arterial blood supply of the lesion.[4] Radiographs show a radiolucent nidus surrounded by reactive radio-density.[1] Radiographic features may differ depending on maturity of the lesion. Histopathologically, three distinct evolutionary stages of ossification have been described. The initial stage is characterised by the presence of actively proliferating, densely packed prominent osteoblasts in a highly vascularised stroma.[4] In the intermediate phase, the osteoid is deposited between the osteoblasts. In the matured stage of the lesion, the osteoid is transformed into well-calcified, compact trabeculae of a typical bone.[5] Surgical excision is the treatment of choice; once the lesion is excised, it does not recur.[4]

A 54-year male presented with the chief complaint of pain and swelling of the right lower back region of the jaw for the last 10 months. The pain was dull and intermittent in nature, aggravated on consumption of meals and lasting for few minutes. Intra-oral examination revealed a bony hard swelling at teeth #47 and #48. The overlying mucosa was normal in color. Tooth #47 was decayed and non-tender on percussion. Intra-oral periapical radiograph revealed multiple patchy radiopaque spots with central areas of radiolucency extending from distal root of tooth #47 to #48 (Figure 1).

Based on radiographic features, differential diagnosis of cementoblastoma, osteoid osteoma, complex odontoma, and ossifying fibroma were considered. Surgical excision of the lesion was done and excised tissue was sent for histopathological examination. The follow-up period of 8 months was uneventful and the pain of the patient was relieved. Histopathological examination of hematoxylin and eosin stained sections revealed multiple trabeculae of mature bone lined by plump osteoblasts with osteocytes inside. Connective tissue stroma was highly vascular and showed numerous dilated blood vessels (Figure 2). Based on histological features, final diagnosis of osteoid osteoma was made.

Osteoid osteoma is a benign tumor of bones which rarely affects jaw bones. A review of literature revealed only 20 cases of osteoid osteomas affecting jaw bones. Presentation of this rare case here, adds to scarity literature on these rare bone lesions.

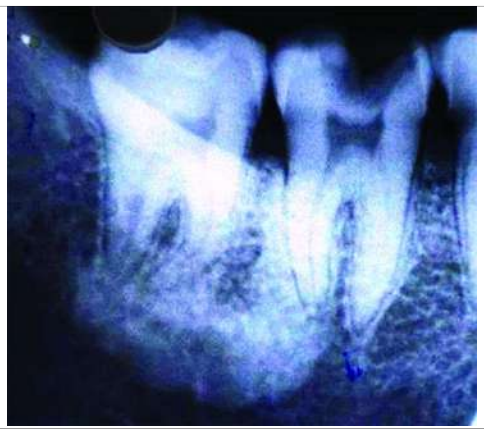

Figure 1: Radiograph reveals radiopaque lesion with few radiolucent areas.

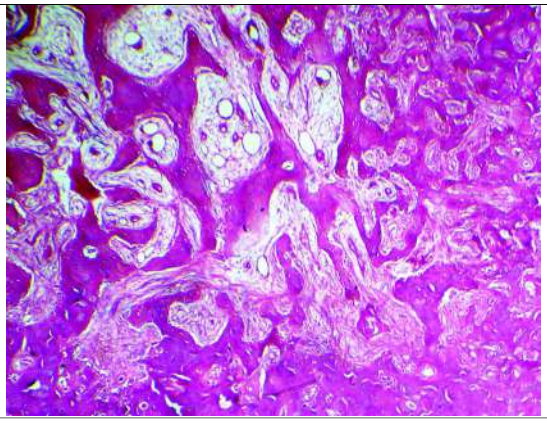

Figure 2: Trabeculae of mature bone with highly vascular stroma .

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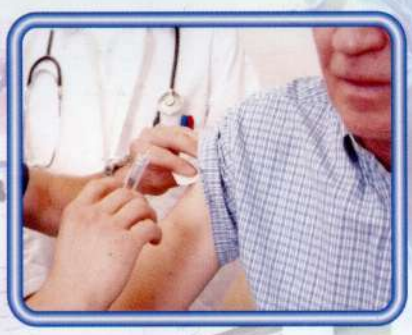

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