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Original Article

Serum Vitamin D and Osteoarthritis

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ABSTRACT

Objective: To determine whether the serum vitamin D level is associated with increasing age in female OA patients.
Study Design: Experimental and Observational Study.
Place and Duration of Study: This study was conducted at the Department of Orthopaedic, Civil Hospital, Karachi from Feb. 2006 to Jan. 2008.
Materials and Methods: Sixty female patients who were suffering from OA were studied. Patients were classified according to their stage of severity of OA in knee joints. Serum vitamin D was measured in serum by ELISA technique.
Results: According to distribution patients of group 3 having the age between 61 – 70 years. Serum vitamin D was detected in serum. Group 3 has high serum Vitamin D levels as compared to group 1 and 2 ($P < 0.5$).
Conclusions: The age group of between 61 years and 70 years has low vitamin D levels, indicating that old age may be one of risk factor for OA.
Key Words: Vitamin D, Age, Osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative disorder of multifactorial etiology characterized by loss of articular cartilage, hypertrophy of bone at the margins, subchondral sclerosis and range of biochemical and morphological alterations of the synovial membrane and joint capsule[1]. OA is the most common casue of musculoskeletal disability depends on the presence of vitamin D. Sub-optimal levels of vitamin D have been shown to have adverse effects on calcium metabolism, osteoblastic activity, matrix ossification, bone density and articular cartilage turn over[2,3]. A study of radiographic knee osteoarthritis showed that low levels of serum and dietary vitamin D were associated with increase in radiographic progression[4]. Vitamin D plays multiple roles that ultimately may have affect on OA. The hormonal form of vitamin D [1, 25 (OH)2 – D] Inhibits collagen synthesis by osteoblasts and promotes bone resorption. Hormonal vitamin D therefore may contribute to OA status in so far as OA is determined by bone mineral density[5].

MATERIALS AND METHODS

The study was conducted on sixty female patients suffering from OA with age group of 41 – 70 years (mean age 55.5 years). The patients were selected on the basis of signs, symptoms, history and severity of disease at particular site and X-Ray of the joints. Patients taking any hormone replacement therapy (HRT), having any metabolic disease, rheumatoid arthritis (RA), gout, systemic lupus erythromatosis (SLE) were excluded from the study. All the subjects answered a questionnaire concerning medical history, present medications, menstrual state and age at menopause. Those with uncertain menstruation history were excluded from the study. The specimens were collected from DOW University of Health Sciences, Karachi, Pakistan.

The patients were divided into three groups. Group 1 have the patients having age 41 to 50 years (Mean age 45.5 years), group 2 having age 51 to 60 years (Mean age 55.5 years), group 3 having age 61 – 70 years (Mean age 65.5 years). A summary grade of radiographic OA was defined for knee joint in terms of the combination of radiographic features present (6, 7). Grade 2 required the presence of either definite osteophytes or joint space narrowing plus 1 other definite features (definite osteophytes or narrowing, or sclerosis, cysts, or deformity grade $\geq$ 1). Grade 3 or greater required the presence of either definite osteophytes or joint space narrowing plus 2 or more other features. We considered grade $\geq$ 2 to represent definite radiographic knee OA (8).
Blood samples were drawn between 08:00 Am and 2:00 PM and serum was immediately frosen (-70 ^{o}C). Vitamin D was estimated by enzyme linked Immunosorbent assay technique, Kat # EIA-4193 supplied by Germany.
Statistical analysis was done by student test. Statistical significance was defined as P value of less than 0.05.

RESULTS

Table 1 shows the characteristics of female knee OA patients. Table 2 shows the age distribution according to radiological classification. Serum Vitamin D levels of group 3 was statistically low ($P < 0.05$) as compared to group I and group 2, as shown in table 3. While radiological staging of OA, according to David classification was shown in table 4.

Table No.1: Characteristics of the Patients

Variable	Mean+SEM
Age (Year)	55.5 $\pm$ 2.50
Duration of menopause (years)	9.4 $\pm$ 1.90
Body Weight (Kg.)	55.6 $\pm$ 1.10
Body mass Index (Kg / m^2)	20.5 $\pm$ 0.92

Table No.2: Age Distribution according to Radiological Classification

Age (Years)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	%age
Group 1 41-50	1	2	7	3	2	10	26.6
Group 2 51-60	-	3	5	9	2	19	26.6
Group 3 61-70	-	1	5	7	12	25	41.6
Percent (%)	1.6	10	28.3	31.6	26.6	100	
Total	1	6	17	19	16	60	100

Table No.3: Status of Serum Vitamin D in Patients in there different Age Groups

Group	Age (Years)	n	Serum Vitamin D	(pg/ml)
1	41-50	(16)	18.10 ± 1.01	
2	51-60	(19)	15.20 ± 0.48	
3	61-70	(25)	*14.92 ± 0.32	

Values are the mean ± S.E.M.

*Values expressed as $P < 0.05$ Significant.

Table No.4: Radiological Staging of QA according to Classification by David (1987)

1.Grade 0	No radiological abnormality.
2.Grade 1	Slight narrowing of joint space, minimum formation of osteophytes and slight sclerosis.
3.Grade 2	Moderate narrowing of joint space, formation of Spurs Sclerosis.
4.Grade 3	Bone changes and sclerosis but not sever loss of bone.
5.Grade 4	Sever sclerosis, loss of bone stock and obliteration of joint.

DISCUSSION

The association of vitamin levels with OA may occur through on effect on either cartilage metabolism or bone metabolism or both. Our study suggest an effect on cartilage metabolosim as indicated radiographically by joint space narrowing. In table 2 we classified the patients in groups, according to their joint grade. According to radiological classification in grade zero 1(1.6%) cases, grade I, 6(10%) cases, grade II, 17 (28.3 %) cases, grade III, 19(13.6%) cases and grade IV, 16 (26.6%) cases. The cases in all grades in respect to age groups between 41 – 50 years : 10(26.6%). The turn over of articaular cartilage is a continuous and tightly coupled process (9). The chondrocytes synthesize both the proteins that make up the articular cartilage matrix and the matrix metalloproteinases enzymes that degrade the cartilage. In normal cartilage this process is tightly coupled such that the same amount of cartilage matrix is synthesized as broken down. However in OA that balance is lost and more degardative enzymes than articular cartilage matrix components are synthesized, which results in loss of cartilage[10] .Other studies have demonstrated that vitamin D is associated with several aspects of articular cartilage metablosim[11,12]. Vitamin D has been shown to stimulate proteglycan synthesis by mature chondrocytes in tissue culture. Also it has been shown to modulate the activity of metalloprotenases enzymes that degrade cartilage (13). Low levels of 1, 25 dihydroxy vitamin D increase metalloproteinases activity (14,15). In our study, therefore low serum levels of vitamin D may have attend the balance of articular cartilage metabolism by increasing production of enzymes and decreasing the synthesis of proteoglycan matrix protein leading to cartilage loss.

CONCLUSION

The age group of between 61 years and 70 years has low vitamin D levels, indicating that old age may be one of risk factor for OA.

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Original Article

Underdiagnosis and the Impact of Headache-related Disability on the Quality of Life Patients

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ABSTRACT

Objective: To determine the extent of under-diagnosis of migraine and the impact of headache-related disability on the quality of life of patients.

Study Design: Prospective, Observational.

Place and Duration of Study: This Study was conducted at the Department of Neurology, Medical Unit II, PUHMS, Nawashah from 1.1.2009 to 31.12.2009.

Methodology: The demographic and clinical data was collected in a proforma. Migraine was diagnosed according to the International Headache Society Classification. Neurological examination and routine laboratory tests were done in all cases. CT Scan of brain was performed whenever deemed necessary. A clinically reliable Migraine Disability Assessment Scale (MIDAS) was administered to the patients with migraine headache. The disability was rated as Grade I (little or no disability) to Grade IV (severe disability) based on the information provided by the patients.

Results: Sixty-eight cases were documented. Male=31, Female=37. Age ranged from 10-59 years. The majority were in the age group of 10-39 years. Fifty-seven (83.8%) had migraine without aura (common migraine) while 11/68 (16.2%) had migraine with aura (classic migraine). In 36/68 (52.9%) nausea was the most frequent associated symptom. Photophobia (17.6%) was more common than phonophobia (5.8%). Visual changes (flashing lights) was the most common associated symptom in migraine with aura. Stress was the most frequent triggering factor in 29.4%. Only 8/68 (11.7%) were previously diagnosed as they were taking some anti-migraine therapy whereas majority 60/68 (88.3%) were newly diagnosed at the time of our assessment. The usual frequency of headache was once/week in 30/68 (44.2%), once/2weeks in 22/68 (32.3%) and once/month in 16/68 (23.5%). Disability was Grade I in 8/68 (11.7%), Grade II in 12/68 (17.6%), Grade III in 30/68 (44.2%) and Grade IV in 18/68 (26.5%). Most of our cases were unaware of their illness nor they were provided relevant information by their physician regarding migraine and its associated aspects.

Conclusions: This study indicate that migraine is under diagnosed in a greater proportion of cases in our region. The headache-related disability caused by migraine adversely affects the quality of life of patients. Unawareness about the disease appears to be the main reason for under diagnosis and increasing disability in our patients.

Key Words: Migraine, Headache, Diagnosis, Disability.

INTRODUCTION

Migraine is a common neurological disorder[1,2]. Approximately 18.% females and 6% males suffer from migraine [2,3] . The prevalence varies with age being highest in 35-45 years old [2]. It is defined as episodic attacks of headache lasting 4 to 74 hours with two of the following symptoms: unilateral pain, throbbing, aggravation on movement, pain of moderate or severe intensity and one of the following associated symptoms: nausea or vomiting, photophobia or phonophobia [4]. The above features are present in patients having migraine without aura (common migraine) whereas those with additional transient focal neurological symptoms usually visual have migraine with aura (classic migraine) [5]. It has been estimated that 64% patients have migraine without aura, 18% have migraine with aura, while 13% have both types of migraine and only 5% have aura without headache [6]. The frequency and duration of headache varies in different individuals. While 10 percent of patients have weekly attacks in 62 percent the attacks occur on a monthly basis [2]. The World Health Organization has listed migraine among the most disabling medical illnesses [7]. The American Migraine Study II [3] indicate that 81% of those suffering from migraine report functional impairment because of headache. While early diagnosis and treatment would help in reducing the disability and the frequency of further episodes, under-diagnosis and under-treatment would deprive the patients of such benefits. Even in developed Western countries migraine remain under diagnosed and under treated [1,2,3]. Given that, the situation is unlikely to be better in our region. We therefore expect more undiagnosed cases and greater degree of disability due to migraine in our patients. The objective of our study was to determine the extent of under-diagnosis of migraine and the impact of headache-related disability on the quality of life of patients.

MATERIALS AND METHODS

The study was conducted at the department of

Neurology in Medical Unit II Peoples University of Medical and Health Sciences for Women, Nawabshah, during 1st January 2009 to 31st December 2009. A total number of 68 patients were included during the study period. Detailed history and clinical examination was documented in a proforma especially designed fro this study. Migraine was diagnosed according to the International Headache Society Classification [4]. Neurological examination and routine laboratory tests were done in all cases. CT Scan of brain was performed whenever deemed necessary. A clinically reliable Migraine Disability Assessment Scale (MIDAS)[8] was administered to the patients. This scale is universally used to grade the disability caused by migraine headache in the last 3 months. The questions were centered on three aspects: (1) Missing job, school or household work due to headache. (2) Loss of productivity at job, school or during household work. (3) Missing family, social or leisure activities because of headache. Depending upon the scores obtained on MIDAS, the disability was graded as Grade I (score 0-5), Grade II (score 6-10), Grade III (score 11-20) and Grade IV (score 21 and above).

RESULTS

Sixty-eight cases were documented. Male=31, Female=37 (Fig. 1). Age ranged from 10-59 years. The majority were in the age group of 10-39 years. Fifty-seven (83.8%) had migraine without aura (common migraine) while 11/68 (16.2%) had migraine with aura (classic migraine) (Table 1). In 36/68 (52.9%) nausea was the most frequent associated symptom.

Table No.1: General characteristics of patients (n=68)

Gender	Number	Percent
Male	31	45.6
Female	37	54.4
Migraine		
Without aura	57	83.8
With aura	11	16.2
Diagnosed		
Previously & taking some anti migraine therapy	8	11.8
Newly diagnosed at the time of assessment	60	88.2
Frequency of headache		
Once / week	30	44.1
Once / 2 week	22	32.4
Once / month	16	23.5

Photophobia 17.6% was more common than phonophobia (5.8%). Visual changes (flashing lights) was the most common associated symptom in migraine with aura patients (16%). Stress was the frequent precipitating factor in 29.4% of the cases. Only 8/68 (11.7%) were previously diagnosed as they were taking some anti-migraine therapy whereas majority 60/68 (88.3%) were newly diagnosed at the time of our assessment. The usual frequency of headache was once/week in 30/68 (44.2%), once/2weeks in 22/68 (32.3%) and once/month in 16/68 (23.5%) (Fig 2). Disability was Grade I in 8/68 (11.7%), Grade II in 12/68 (17.6%), Grade III in 30/68 (44.2%) and Grade IV in 18/68 (26.5%) (Table 2). Most of our cases were unaware of their illness nor they were provided relevant information by their physician regarding migraine and its associated aspects.

Table No.2: Disability (n=68)

Disability	Number	Percent
Grade I	8	11.8
Grade II	12	17.6
Grade III	30	44.1
Grade IV	18	26.5

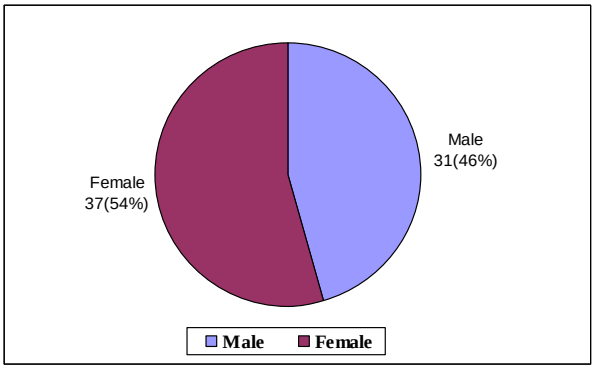

Figure 1: Gender distribution

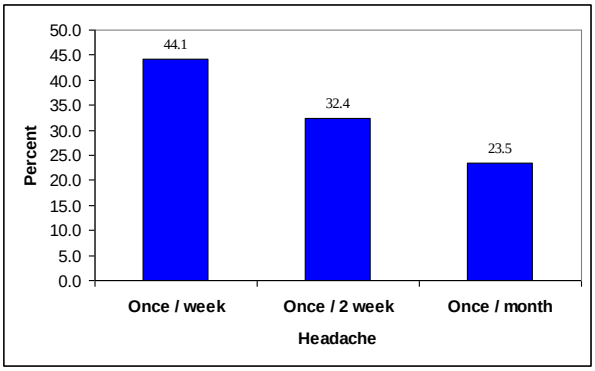

Figure 2: Frequency of Headache

DISCUSSION

We studied the extent of under-diagnosis of migraine and the impact of headache-related disability on the quality of life of patients. The disability in majority of our patients ranged from moderate Grade III (score 11-20) to severe Grade IV (score 21+). Male and female were almost equally affected and the disability in both sexes was comparable. Studies done in the developed Western countries have shown that migraine is more common in females (18%) than in males (6%) and that it is also more disabling in females than in males [3]. This is inconsistent with our findings. We found no marked

gender differences. One reason for this discrepancy could be the small size of our study. Another possibility may the cultural differences where women in our culture are less likely to be involved in the office-work compared to those in the Western countries. Women in our part of the world mostly bear the burden of household work whereas a significant proportion of women in the Western world have double the work load (household + office work). That we believe could account for a greater headache-related disability among females in Western countries compared to that of ours.

In our study the most common age-range affected was 10-39 years. The reported highest prevalence is in the age-group 35-45 years [3]. These differences are likely due to the population variations [9] where the proportion of younger segment of our population is increasing whereas in Western countries the older population is increasing.

Migraine without aura was more common (83.8%) than migraine with aura (16.2%) which is consistent with the previously published reports [5]. However, under-diagnosis was a major issue as the majority of our patients (88.3%) were not diagnosed prior to our assessment and only 11.7% were on some anti-migraine therapy suggesting that they were previously diagnosed. The American Migraine study [3] reported that only 38% of cases were ever diagnosed by a physician which means that 62% of the cases remained undiagnosed even in the developed countries. Our figure of 88% undiagnosed cases compared to reported 62% is obviously quite high but not surprising. It could either be due lack of diagnostic ability on the part of physicians or more likely due to lack of awareness about this illness in the general population. It is conceivable that people in our region do not consider migraine as a disease which require proper consultation and treatment. Since the majority of migraineurs get relief by taking over-the-counter analgesics [10], they tend to avoid seeing a physician who would otherwise charge fees and ask them to go for various laboratory tests. However, increasing frequency of headaches may compel them to seek medical treatment. This is evident in our data as the large number of our cases (44.2%) had usual frequency of one episode per week compared to the reported frequency of once per week in only 10% of the cases [2]. Furthermore, migraine is episodic, the pain-related disability is usually reversible and self limiting once the episode is over, but the fear of another episode of headache remains and this may further add to the agony and uncertainty [11]. That may be another reason for seeking medical treatment. Interestingly, the majority of our patients were headache-free at the time of assessment but they were concerned about the future episodes.

According to WHO migraine is one of the most disabling illnesses [7]. It has been estimated that in 50% of the migraine sufferers there is 90% work loss due to headache-related disability [3]. In American Migraine Study II [2], 51% reported work or school activity reduction by more than 50%. This is almost close to 44% of our cases who had similar reduction. In the same study [2], 53% reported severe headache causing extreme impairment in activities requiring bed rest. The same degree of impairment was present in 26% of our cases which is lower than reported (53%). The reason for this is not clear. The younger age of onset in our patients may account for these differences as younger individuals are more likely to be resilient to pain compared to the older individuals. Indeed, there are reports indicating that age, among other factors, may influence the threshold for migraine [12]. Moreover, stress as a precipitating factor was present in 29.4% of our cases which is lower than that reported by Robins (62%) [13] and even much lower than reported in a local hospital-based study by Shehbaz et al (90%) [14]. It is interesting to note that these studies [13,14] were done at the urban centers whereas at our centre patients were mostly from the rural areas. This may represent the rural-urban differences where people in the urban areas are more prone to stress compared to those living in rural areas. Identification of co-morbid psychiatric illness in migraineurs is however important as these may have added adverse impact on the quality of life of patients [14,15]. The functional impairment caused by migraine may have broader consequences not for the affected individuals only but for the society as a whole. Currently better therapeutic options are available for the acute treatment and prophylaxis of migraine [16]. It is therefore imperative that the awareness about this disease be enhanced among the general physicians and the public at large so that the therapeutic benefits can be derived sooner.

CONCLUSIONS

This study indicates that migraine is under diagnosed in a greater proportion of cases in our region. The headache-related disability caused by migraine adversely affects the quality of life of patients. Unawareness about the disease appears to be the main reason for under diagnosis and increasing disability in our patients.

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Original Article

Induced Abortion – A Continuing Threat to Maternal Life

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ABSTRACT

Background: In Pakistan, therapeutic induced abortion is a controversial issue and continued to be a significant contributor of maternal mortality and morbidity. The aim of the present study is to assess the magnitude of septic abortion in a tertiary care hospital over a period of 2 years with special emphasis on maternal mortality and morbidity.

Objectives: This prospective study was aimed to determine the frequency of induced abortion, to know the reason for requesting abortion, assess the associated maternal morbidity and mortality in our setup.

Study Design: Descriptive Study.

Place and Duration of Study: This Study was conducted at the Department of OBGY, PUMHSW Nawabshah from 1st January 2009 to 31st December 2010.

Materials and Methods: Hospital record of patients who were admitted with unsafe abortions in 2 years (2009 – 2010) were reviewed to evaluate the demographic and clinical profile in relation to age, parity, marital status, indication and method of abortion, qualification of abortion provider and maternal mortality.

Result: Unsafe abortion contributes 4.4 % of total patients admitted with abortion over 2 years. Mean age of them was found ± SD 30.14 + 8.56 and mean parity was 6.07 ± 3.00. 78.6 % patients belong to poor community and > 70 % patients were married and used it as a method of contraception. Uterine instrumentation was the commonest method (78 %) used to induce abortion.

Majority of women were admitted with life threatening complications like haemorrhage (75 %), sepsis (53.57 %), hypovolumic shock (39.28 %) and faecal peritonitis in 21.42 %. DIC in 10.71 %, uterine perforation in 28.57 % and mortality in 4 (14.28 %). 5 (17.85 %) were managed conservatively, 13 (46.42 %) had re-evacuation, 10 patients had exploratory laparotomy, out of them 2 needed peritoneum toilet, while in 5 patients gut resection and anastomosis and in one permanent colostomy was done. Uterine trauma found in 8 patients (28.57 %) in whom 3 (10.70 %) ended up in hysterectomy. Unsafe abortion contribute 14.28 % of death in study group.

Conclusion: The present study conclude that unsafe abortion is a major neglected health issue needs attention and high degree of commitment. Its elimination requires advocacy, policies to support woman right and improving access to family planning services.

Key Words: Unsafe abortion, maternal mortality, ECP, Pakistan.

INTRODUCTION

Induced abortion is a major public health issue even in countries where it is legal. WHO defines unsafe induced abortion as the one when unintended pregnancy is terminated either by the person lacking necessary skill or is performed in an environment lacking minimal medical standard or both[1]. Septic induced abortion is a significant contributor in maternal mortality in developing areas of world. Maternal mortality is a sensitive index of judging standards of obstetrical care, maternal and neonatal health and socioeconomic status of a country. It is estimated that > 600,000 maternal deaths occur each year, > 99 % of these deaths occur in the developing countries, which account for about 85 % of world birth[2,3]. Each year 46 million women throughout the world undergo abortion, 20 million in the countries where abortion is either restricted or illegal[3], WHO estimate that in these 20 million women, 70,000 die while million suffer chronic morbidities[4,5].

In Pakistan, abortion is considered to be legal only when it is carried out to save the life of the mother or to provide necessary treatment to her[6]. An estimated 890,000 abortions performed annually in Pakistan, with an abortion rate of 29/1000 women of reproductive age[7,8,9]. Unsafe abortions contribute 13 % of maternal deaths in Pakistan[10]. It is very difficult to estimate the exact magnitude of the problem because of under reporting and most of time only the patient with life threatening complication reach the tertiary hospital for treatment.

MATERIALS AND METHODS

This was a descriptive study of patients admitted with clinical situation of septic abortion during a period from January 2009 to December 2010 at Department of Obstetrics & Gynaecology, Peoples University of Medical & Health Sciences for Women Hospital Nawabshah. Being a tertiary and only referral hospital,

we receive those patients who were not manageable at peripheral level.

The data was collected from hospital record and all patients were analysed by detailed history, physical and biochemical examination including CBC, LFT, RFT, serum electrolyte and coagulation profile and high vaginal swab for C/S. Chest x-ray and detailed ultrasound examination for assessment for RPOCs and extent of trauma were carried out. X-ray abdomen erect postures in all suspected cases of intestinal perforation were performed. Patients were managed according to their clinical situation and treatment was provided in collaboration with other departments. Data was entered into SPSS version 10.0 and analysed.

RESULTS

The total number of gynaecological admissions during the study period was 2811, among them 636 (22.62 %) patients were presented with abortion. 28 (4.4 %) cases of induced abortion were admitted during this period.
Age ranges of patients were between 15 – 45 years, the mean age ± SD was 30.14 ± 8.56. Mean parity ± SD was 6.07 ±300. Majority of patients 60.7 % underwent abortion in the first trimester, 21.42 % had it in the early second trimester while in 7.1 % it was attempted after 20 weeks.

Table No. 1: Demographic Characteristics of Patients

Characteristic	No. of Patients	Percentage
Age Group		
15 – 25 Years	06	21.42 %
26 – 35 Years	17	60.71 %
36 – 45 Years	05	17.85 %
Parity		
0	03	10.70 %
1 – 4	02	7.14 %
5 – 8	16	57.14 %
> 8	07	25 %
Marital Status		
Unmarried	03	10.71 %
Married	20	71.42 %
Widow	05	17.85 %
Gestational age (Wks)		
Not Known	03	10.7 %
< 12 Weeks	17	60.7 %
13 – 20 Weeks	06	21.42 %
> 20 Weeks	02	7.14 %
Socioeconomic Status		
Poor	22	78.57 %
Middle class	06	21.42 %
Well Family	None	---

Most of patients (78.6 %) were belonged to poor community. While evaluating the reason for abortion, 18 (64.28 %) patients used it as a method of contraception, 3 (10.7 %) were unmarried, female gender was the reason in 2 (7.14 %) while 5 widows used it as a method to get rid of unwanted pregnancies.
D & C was the preferred method in 22 (78 %) followed by local medication in 4 (14.28 %) and herbal sticks in 2 (7.14 %) patients.

Table No. 2:Reasons for Seeking Abortion

Reason	No. of Patients	Percentage
Unmarried	03	10.71 %
Widow	05	17.85 %
Contraceptive Method	18	64.28 %
Female Gender	02	7.14 %

Table No. 3:Patients Presentation

Presentation	No. of Patients	Percentage
Vaginal Bleeding	21	75 %
Septicemia	15	53.57 %
Hypovolumic Shock	11	39.28 %
Uterine Trauma	08	28.57 %
Faecal Peritonitis	06	21.42 %
DIC	03	10.71 %
Expired	04	14.28 %

Table No. 4:Distribution of Management Options

Presentation	No. of Patients	Percentage
SURGICAL INTERVENTION		
Evacuation of Uterus	13	46.42 %
Laparotomy	**10**	**35.71 %**
Drainage of Pus + Peritoneal Toilet	02	7.14 %
Hysterectomy	02	7.14 %
Hysterectomy with Gut repair	01	3.57 %
Uterine repair with resection and anastomosis	04	14.28 %
Uterine repair with permanent colostomy	01	3.57 %
CONSERVATIVE		
Conservative treatment	05	17.85 %

Regarding healthcare providers, abortion induced by doctors in 11 (39.28 %) cases, Dias in 9 (32.14 %) and midwives in 8 (28.57 %) of cases
Concerning with clinical presentation, 15 (53.57 %) patients were presented with sepsis, 21 (75 %) patients with vaginal bleeding, 11 (39.28 %) patients with hypovolumic shock and 6 (21.42 %) patients with faecal peritonitis.
Features of DIC seen in 3 (10.71 %) patients. Uterine trauma was found in 8 (28.57 %) patients, while 4 (14.28 %) were expired.
All the patients received broad spectrum antibiotic coverage and blood transfusions, 13 (46.42 %) needed evacuation for RPOCs, while 5 (17.85 %) were

managed conservatively. 10 patients ended up in laparotomy, out of them 2 (7.14 %) had abdominal collection and 8 (28.57 %) for uterine perforation. Uterine perforation was repaired in 5 (17.85 %) patients while 3 (10.70 %) ended up in hysterectomy. 6 (21.42 %) patients had associated gut injuries, 5 (7.85 %) needed resection and anastomosis, while one (3.57 %) patient ended up in permanent colostomy. 3 (10.7 %) patients presented with septicemia and DIC, have vaginal bleeding and died within 24 hours. One (3.57%) patient died due to overt sepsis and multiorgan failure.

DISCUSSION

Worldwide, millions of women seek induced abortion which remains a secret if successful otherwise lead to maternal death, serious health morbidities and long term consequences in affected women.

Unsafe abortion is a totally preventable problem but due to declining attitude of community towards contraception along with its poor availability as well as restrictive abortion law, it remains a major health issue.

The overall abortion rate declined in the past years, but the proportion of unsafe abortion has increased from 44 – 47 %. Worldwide 48 % of all abortions are unsafe, in Africa and Latin America 95 % and in Asia 60 % abortions are unsafe[11]. In Pakistan, the rate of induced abortion was 29/1000 women in which 6.4/1000 were hospitalized due to abortion complications[12], putting an extra burden over already compromised health sector and economy of the country.

The frequency of induced abortion in current study is 4.4 % almost comparable with 4.7 %[13] and 3.7 %[14] respectively in other studies from different parts of Pakistan.

3/4 of the study population was between 26 – 35 years and > 50 % was grand multiparae using it as a contraceptive method almost correlating with the results of SZ study[15]. Association of marital status as a risk factor found in > 70 % of study population as in other studies in Pakistan[16,17]. Premarital sexual activity is strictly prohibited in our society, only 10 % of unmarried girls suffered unsafe abortion consistent with data from other studies[18,19]. Situation is totally different in developed countries, in USA > 50 % of women under going induced abortion were < 25 years[20] and 2/3rd were never married[21].

The significant groups of women need attention were 5 widows in whom 3 pregnancies were the result of sexual assault by their caretaker and 2 were due to extreme poverty. This segment of community particularly need an awareness of emergency contraception which effectively reduces the number of unintended pregnancies and substantially causes an 11 % decline in induced abortion rate[22].

78 % of study population comprised of poor socioeconomic class while remaining were from low middle class indicating a high risk group for development of complications. Majority of our women (60.71 %) sought abortion in the first trimester similar to other studies[10,17]. Abortion providers were doctors in 39.28 % cases, while great majority (60 %) were carried out by Dias and Midwives. These figures indicated an easy accessibility of unqualified personnel and confidence of client on them.

In current study haemorrhage was the main complication (75 %) comparable with other studies[18,19]. Septicemia was found in > 50 % of cases reflecting the poor circumstances in which abortions were performed. The most drastic complication in the study group was uterine trauma (28.57 %) along with gut perforation in 21.42 % patients. 82.14 % patients required surgical interventions These women suffer major morbidities like hysterectomy in 3 (10.7 %) and permanent colostomy in one (3.57 %) apart from their long term impact.

Unsafe abortion responsible was responsible for 14.28 % of deaths in the study group and the septicemia was the main reason behind.

CONCLUSION

The data of present study confirms that unsafe abortion is a major health issue needs a high degree of commitment from all categories of health professionals and community. Its elimination requires advocacy program aim at both reforming the laws and policies to support women rights and improving access to family planning and abortion related services along with provision of abortion by skilled healthcare providers with PAC (Post Abortion Care).

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Original Article

Diffusion Weighted Magnetic Resonance imaging in the Diagnosis and Management of Acute Stroke

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ABSTRACT

Objective: To evaluate the diagnostic accuracy of diffusion –weighted magnetic resonance (MR) imaging performed within 6 hours of the onset of stroke symptoms

Study Design: Cross sectional study.

Place and Duration of Study: This study was conducted at the Department of Radiology Nishtar Medical College & Hospital Multan from August, 2010 to August, 2011.

Patients and Methods: Diffusion weighted MR imaging, along with conventional MR imaging performed in 36 patients who presented with acute stroke like symptoms within 6 hours of onset of symptoms. Diagnosis was noted. Patients admitted in medical ward. Follow up MR was performed after one weak. Findings compared with initial scan. Diffusion weighted MR and conventional MR diagnosis was compared with final clinical diagnosis. Sensitivities and specificities of diffusion weighted and conventional MR imaging (FLAIR, T2-w) noted comparing with final clinical diagnosis

Results: Diffusion weighted MR imaging indicated stroke in 30 patients, all of whom had a final diagnosis of acute stroke Diffusion weighted images were negative in six patients, all of whom had a final clinical diagnosis other than stroke (100% sensitivity ,100% specificity).FLAIR images detected infarcts in 25 patients within 6hours of onset of symptoms out of 30 patients having stroke on final diagnosis(83% sensitivity,100% specificity).T2-w images detected infarcts in 22 patients on initial scan with sensitivity of 73% and specificity of 100%.

Conclusion: Diffusion weighted MR imaging is highly accurate for diagnosing acute ischemic stroke within 6 hours of symptoms onset and is superior to conventional MR imaging.

Key Words: Diffusion weighted imaging (DWI), Fluid attenuation inversion recovery (FLAIR), T2-w imaging.

INTRODUCTION

The advent of thrombolytic and neuro-protective agents has intensified the need for an accurate and timely diagnosis of acute ischemic brain injury. Efforts expended in the emergency department to gain optimal management of acute stroke during its earliest stages could be substantially improved with accurate information about the presence or absence of ischemic brain injury[1,2].

During early evolution of cerebral infarction, computed tomography (CT) and conventional magnetic resonance (MR) imaging remain problematic. Diffusion-weighted MR imaging is very sensitive to an early pathophysiological process in cerebral infarction[3].

Cytotoxic edema, which is caused by the accumulation of intracellular water due to cell membrane damage minutes after onset of acute cerebral ischemia, causes a restriction of microscopic proton diffusion[4,5]. In diffusion–weighted MRI, this decrease in water diffusion is presumably reflected in a decrease of the apparent diffusion coefficient (ADC) on ADC trace maps, which is visualized as a hyperintensity on the diffusion weighted images (DWI).Previous studies showed that DWI is able to visualized cerebral ischemic changes within 5 minutes to 1 to 3 hours after onset of symptoms[6]. Other advantages of DWI are the low number of false negative investigations (5%), the clear discrimination between ischemic lesions and non ischemic brain, and the discrimination between acute and chronic ischemic lesions. With these features, DWI facilitates the determination of the type, site, and extent of cerebral ischemia at an early stage. This might help to predict the clinical outcome of stroke patient[7-8].

Recent studies showed that in the acute stage after stroke, DWI is more sensitive for early ischemic changes than T2-w MRI.However, other studies showed that both PD-w imaging and fluid attenuation inversion recovery (FLAIR) imaging are superior to T2-w imaging in the detection of acute ischemic lesions. Therefore, DWI should be compared with T2-w and FLAIR imaging as well.

MATERIALS AND METHODS

Study was conducted from August, 2010 to August 2011 to compare the diagnostic accuracy of diffusion weighted magnetic resonance imaging with conventional magnetic resonance imaging in patients

with acute stroke presenting within 6 hours of onset of symptoms

Total of 36 patients underwent emergency MRI with clinical suspicion of ischemic stroke for less than 6 hours of stroke symptoms and in which emergency CT scan was negative for hemorrhage

MRI was performed according to acute stroke departmental protocol with 1.5 Tesla clinical imaging system (Philips Medical System) .Multiplanner multiecho imaging was performed including conventional imaging (T1-w, T2-w and FLAIR) and diffusion weighted imaging.MR images were interpreted by senior consultant radiologist and diagnosis was recorded in every patient.

Follow up MRI brain was performed after one week of symptoms and radiological diagnosis was also recorded

Findings of initial MR imaging, follow up MR and clinical diagnosis were analyzed statistically to compare the accuracy of diffusion weighted imaging with conventional MR imaging taking clinical diagnosis as gold standard

RESULTS

From total of 36 patients, 20(55%) were male and 16(45%) were females. The mean age was 55 years

Out of 36 patients, who underwent for emergency MR imaging.DW-imaging detected ischemic lesions in 30 patients that were confirmed on follow up MR scan and final clinical diagnosis showing 100 % sensitivity , specificity and diagnostic accuracy. Six patients out of 36 showed alternate diagnosis both on MR imaging and on discharge chart.

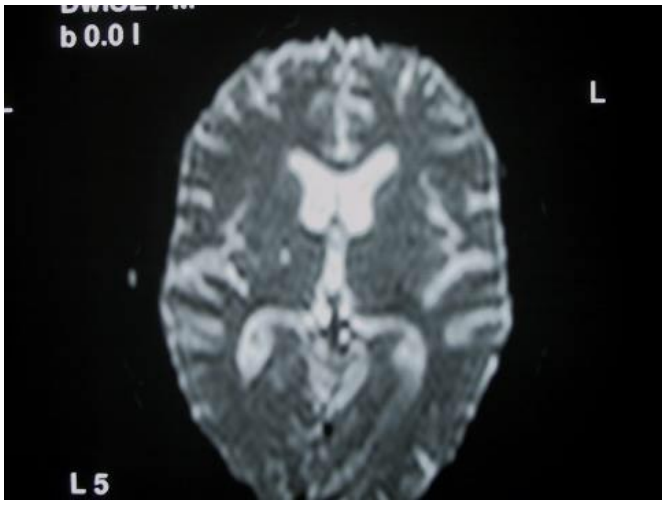
Table NO.1: Comparison of DWI, T2-w and FLAIR imaging with clinical outcome (final diagnosis) (n=36)

Imaging Findings	Clinical outcome	
	Stroke	**No Stroke**
Diffusion Weighted MR-imaging		
Stroke	30	0
No Stroke	0	0
FLAIR Imaging		
Stroke	25	0
No Stroke	05	6
T2-weighted Imaging		
Stroke	22	0
No Stroke	08	6

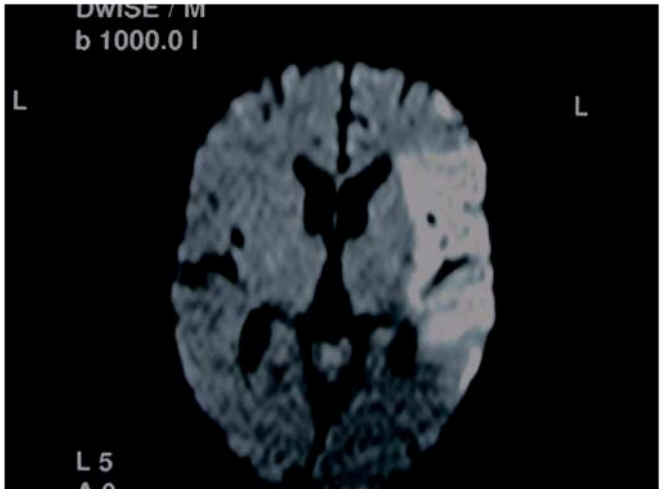
Note-The sensitivities and specificities were 100% and 100% for diffusion weighted MR imaging;83% and 100% for FLAIR imaging and 73% and 100% for T2-w MR imaging

Flair imaging detected ischemic lesions in 25 patients on initial MR scans done within 6 hours of onset of symptoms showing sensitivity, specificity and diagnostic accuracy of 83%, 100% and 86% respectively.

T2-w imaging detected ischemic lesions in 22 patients on initial MR imaging done within 6 hours of onset of symptoms showing sensitivity, specificity and diagnostic accuracy of 73%,100% and % respectively.



T2-w image showing no ischemic lesion in a 55 yrs patient with an acute right sided hemiparesis within 6hrs of onset of symptoms. (Fig-1)



Diffusion weighted (DW) image showing hyperintensity along left MCA territory in a 55 yrs patient with an acute right sided hemiparesis within 6hrs of symptoms onset.(Fig-2)

DISCUSSION

During one year period, we performed diffusion weighted MR imaging within 6 hours of symptoms onset in 36 patients who presented with a new neurological deficit of sufficient severity to require hospitalization. Diffusion weighted MR imaging enabled the accurate diagnosis of acute stroke in 30 patients and helped exclude stroke in six. We found

diffusion weighted MR imaging to be significantly superior to conventional MR imaging (FLAIR and T2-weighted imaging) in the diagnosis of hyperacute stroke[9,10].

Although there have been several studies about diffusion –weighted MR imaging of patient with acute stroke, this study is different in several important ways. The results of our investigation help confirm those of previous studies, which suggested the high sensitivity of diffusion –weighted imaging in acute cerebral infarction[10-11]. We evaluated all patients who presented emergently during 1 year of study period, were admitted because of their stroke like symptoms, and underwent diffusion weighted MR imaging in which patients were imaged within 6 hours of onset of stroke like symptoms. Our study provides comparison of diffusion weighted imaging with conventional MR imaging.

Our findings suggest that diffusion weighted MR imaging has the potential to make another contribution to acute stroke management. A negative diffusion weighted image is highly accurate in the exclusion of most acute cerebral infarctions[12]. The exception may be very small penetrator artery infarcts in the brain stem. The high accuracy of diffusion weighted MR imaging in excluding the probability of stroke could have a substantial effect on the treatment of patients who present with acute onset of stroke like symptoms. In many circumstances, a negative diffusion –weighted MR imaging may spare patients prolonged and health care resources and help ensure the likelihood that treatment regimens are appropriately matched to patients need[13, 14].

An area of great interest in acute stroke imaging is the appearance of transient ischemic attacks (TIA) at diffusion weighted imaging in six patients with a negative diffusion weighted MR image; transient ischemic attack was the final diagnosis. This suggest that diffusion weighted MR imaging is insensitive to transient ischemia, even though it may be sufficiently severe to produce symptoms[15-16].

Diffusion weighted MR imaging provides information that is fundamentally different than that available with CT or conventional MR imaging. In acute ischemic stroke, CT and conventional MR imaging demonstrate changes that are largely depended on same physiological parameter; an increase in tissue water. This results in hypoattenuation and loss of gray-white matter differentiation on CT scan and hyperintensity on T2w and FLAIR images. In distinction to these modalities, diffusion weighted MR imaging can depict Cytotoxic edema. This pathophysiological event occurs very early as adenosine triphosphate level decrease in ischemic brain, although this explanation for the high contrast signal abnormality observed in acute infarction at diffusion weighted imaging is somewhat controversial, all studies reported to date consistent with the presence of Cytotoxic edema as a significant contributing factor to the abnormal signal[17,18].

CONCLUSION

In conclusion, we have found, under clinical circumstances that diffusion weighted MR imaging of the brain is highly accurate in the diagnosis of acute stroke and provides superior lesion contrast compared with that of CT and conventional MR imaging. Our results indicate that diffusion weighted MR imaging may have important role in the treatment of patients who presents with new onset of stroke like neurological deficit.

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Original Article

Clinical Presentation and Drug Resistance Patterns of Salmonellae Typhi and Paratyphi at a Tertiary Care Hospital of Sindh

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ABSTRACT

Objective: The aim of this study is to evaluate the clinical presentation and drug resistance patterns of Salmonellae typhi & paratyphi

Study design: Observational Descriptive Study.

Place and Duration: This study was conducted at the Muhammad Medical Hospital Mirpurkhas, from Jan 2010 to April 2011.

Materials and Methods: One hundred twenty six patients were studied, who satisfied the clinical and laboratory criteria of typhoid/paratyphoid fever. The blood samples, 5–10 ml from adults were inoculated directly into blood culture bottles. Subcultures were also performed. Antibiotic sensitivity was tested by the Kirby–Bauer technique according to Clinical and Laboratory Standards Institute guidelines. Statistical analysis was performed on SPSS version 10.0. (Chicago, Illinosis, USA), using the chi-square test and student's t-test for the qualitative and quantitative variables respectively.

Results: The identified organisms were S.typhi observed in 91 (72.22%), both S typhi/paratyphi in 18 (14.28%) and S.paratyphi A and B in the rest 17 (13.49%). In 97 (76.98%) of patients, antibody O titers were ≥1:160 and in 39 (30.95%) titers were <1:160. The overall multi-drug resistant isolates were found in >80% for the first line agent's i.e.; ampicillin, amoxicillin, cotrimoxazole and chloramphenicol. The highest sensitivity rate was found for the cefixime (98.41%) and the lowest one for the ampicillin (22.2%).

Conclusions: We found drug resistant and multi-drug resistant salmonellae in our study; this may be because of antibiotic use as self medication, medication by pharmacist and quacks

Key words: Salmonella typhi/ paratyphi, typhoid fever, drug resistance

INTRODUCTION

Enteric fever is a clinical syndrome characterized by constitutional and gastrointestinal symptoms and by headache. It can be caused by any Salmonella species. The term typhoid fever applies when serotype typhi is the cause. Infection is transmitted by consumption of contaminated food or drink. The incubation period is 5-14 days.[1] Pakistan is a hyper-endemic area for typhoid fever. According to WHO 2008 report the incidence of typhoid fever in 5-15 years children was 412 per million in 2002.[2] Early gastrointestinal manifestations include constipation, mild diarrhoea and abdominal pain. Approximately 50% of patients have hepatosplenomegaly and upto 3-10% develop intestinal perforation.[3] A definitive diagnosis of typhoid fever can be made by isolation of Salmonella.typhi (S.typhi) or paratyphi from samples of blood, bone marrow, urine, stool, rose spots or intestinal secretions, and it is regarded as "gold standard method". While the alternative diagnostic methods include serologic testing. However, in countries where typhoid fever is endemic, the specificity of serologic tests is not reliable.[4] The introduction of chloramphenicol since 1948 reduced the mortality rate to 4%. In the developing countries where effective antibiotics are not readily accessible to public, martlaity rates reach upto 10%, while the mortality rate in the developed countries hardly reaches 1%.[5] Due to the increasing resistance to traditional antibacterial drugs used for therapy (ampicillin, amoxicillin, co-trimoxazole and chloramphenicol), the fluoroquinolones; such as the ciprofloxacin and ofloxacin became the drugs of choice for the treatment of these infections.[6] The quinolone were reported to be effective in the treatment of adults with multidrug resistant typhoid with cure rates of 100% and third generation cephalosporins having 82-97% cure rates.[7] But a number of resistance mechanisms to quinolone in certain parts of the world led to decreased susceptibility of S. typhi to these agents.[6] Like many tropical areas, typhoid fever remains major public health problem in Sindh, and this compelled us to conduct a prospective study on clinical presentation and drug resistance patterns of typhoid/paratyphoid fever at a tertiary care hospital.

MATERIALS AND METHODS

Patients with a clinical diagnosis suggestive of typhoid fever,admitted at Muhammad Medical College Hospital

Mirpurkhas, Sindh from Jan 2010 to April 2011, were enrolled in the study. A detailed clinical and treatment history was elicited from all the patients. The full blood counts, Widal tests, Liver function tests and roentgenography were ordered. A case of enteric fever/typhoid fever was defined as an isolation of S typhi/paratyphi A and B from a sample of blood in a hospitalized patient. Blood samples were collected from febrile patients whether taking or not an antibiotic therapy. The blood samples, 5–10 ml from adults were collected by venepuncture using aseptic technique, and inoculated directly into blood culture bottles containing 50 ml brain heart infusion broth. The samples were processed according to standard recommended techniques.[8] The bottles were incubated at 37ºC for 7 days and examined daily for bacterial growth. Subcultures were performed on the first, second, third, fifth and seventh day of incubation on 5% sheep blood agar and MacConkey agar.[9] Suspected non-lactose fermenting colonies were screened biochemically and their identity was confirmed serologically. Antibiotic sensitivity was tested by the Kirby–Bauer technique according to Clinical and Laboratory Standards Institute guidelines.[10] The following antibiotics were used: chloramphenicol (30ug), nalidixic acid (30ug), ampicillin (10ug), amoxicillin (10ug), amoxicillin/clavulanic acid (20/10ug), co-trimoxazole (25ug), ciprofloxacin (5 ug), ofloxacin (5ug), cefotaxime (10ug), ceftriaxone (10ug), cefpodoxime (30ug), sparfloxacin (5ug), azithromycin (15ug) levofloxacin (5ug), and cefixime (10ug). The study was approved by the ethics committee of institute. Statistical analysis was performed on SPSS version 10.0. (Chicago, Illinosis, USA), using the chi-square test and student's t-test for the qualitative and quantitative variables respectively.

RESULTS

A total 126 patients including 59 male and 67 female, were studied. Clinical features at the time of presentation are shown in table I. The highest incidence rate for enteric fever was observed from August through November. Most of the patients were in their 2nd and 3rd decade (38.5% and 41.8%). The identified organisms were S.typhi observed in 91 (72.22%), both S typhi/paratyphi in 18 (14.28%) and S.paratyphi A and B in the other 17 (13.49%) patients. In 97 (76.98%), antibody O titers were ≥1:160 and in 39 (30.95%) titers were <1:160. The drug resistance was observed to one or the other agent. The overall multi-drug resistant isolates were found in >80% for the first line agent's i.e; ampicillin, amoxicillin, cotrimoxazole and chloramphenicol. The highest sensitivity rate was found for the cefixime (98.41%) and the lowest one for the ampicillin (22.2%). The drug sensitivity and resistance patterns are shown in table II. Upto 30% of patients were taking one or the other of the first line antibiotics as self medication, were running fever, and blood cultures were found positive in 70% of them. Liver function tests were altered in 37.30% of patient. Mean bilirubin and SGPT levels were 1.9±0.38 mg/dl and 59±31U respectively. Full blood counts revealed leukopenia in 74 (58.73%) and leukocytosis in 12 (9.52%).

Table No. 1: Clinical features at the time of presentation (n=126)

	No.	%
Fever	126	100
Chills	95	79.39
Headache	98	77.7
Anorexia	107	84.9
Abdominal pain	27	21.4
Diarrhoea	19	15.0
Constipation	39	30.9
Vomiting	57	45.2
Splenomegaly	71	56.3
Bloody diarrhoea	13	10.3
Leukopenia	74	58.7
Rose spots	19	15.0
Epistaxis	03	02.3
Sore throat	37	29.3
Respiratory symptoms	61	48.4
Meningism	53	40.0
Hepatomegaly	09	07.1
Coated tongue	09	07.1
Disorientation	45	35.7

Table No.2: Antibiotic sensitivity and resistance patterns (n=126)

Antibiotic	Sensitivity (%)		
	Sensitive (%)	Inter-mediate (%)	Resis-tance (%)
Ampicillin (10*u*g)	11.1	11.1	77.7
Amoxicillin (10*u*g)	22.2	9.52	76.19
Amoxi-Clav (20/10*u*g)	37.3	7.14	55.5
Chloramphenicol (30*u*g)	15.07	21.42	63.49
Nalidixic Acid (30*u*g)	19.04	23.01	57.93
Co-Trimoxazole (25*u*g)	16.6	13.49	69.84
Ciprofloxacin (5*ug*)	29.36	15.07	63.49
Ofloxacin (5*u*g)	24.60	16.66	58.73
Cefotaxime (10*u*g)	47.61	05.55	46.82
Ceftriaxone (10*u*g)	53.17	18.25	28.57
Cefpodoxime (30*u*g)	78.57	07.93	13.49
Sparfloxacin (5*u*g)	80.95	04.76	14.28
Azithromycin (15*u*g)	88.8	06.34	03.96
Levofloxacin (5*u*g)	95.23	02.38	02.38
Cefixime(10*u*g)	96.03	02.38	01.58

DISCUSSION

The antimicrobial resistance of S.typhi was rare prior to the 1980s. Chloramphenicol was the treatment of choice, but in the 1980s, resistance to chloramphenicol and alternative agents began to emerge in countries

where S.typhi was endemic. Thus ciprofloxacin became drug of choice for typhoid despite limitations to widespread use. Strains of S.typhi resistant to chloramphenicol, ampicillin, and co-trimoxazole were reported in South America, the Indian subcontinent, Africa and Saudi Arabia. At the same time, in Southern Vietnam, the multi-drug resistance became established by the early 1990s. Shortly after, isolates of S.typhi with reduced susceptibility to quinolone began to appear from the same areas with resistance to first line drugs, thereby threatening these agents for treatment of typhoid fever. Strains of S.typhi with decreased susceptibility to ciprofloxacin and resistant to nalidixic acid increased to 23% in the UK in 1999s, mainly in patients returning from travel to Asia who did not respond well to treatment with fluoroquinolones antimicrobials.[6] A recent prospective population based study in five Asian countries confirmed that S.typhi resistance to Nalidixic acid is greater than 50% in both India and Pakistan. Our result of 57.93% Nalidixic acid resistance is comparable with this study.[11] Our study shows that >80% of S.typh/paratyphii were multi drug resistant; (resistance to the chloramphenicol, ampicillin and cotrimoxazole). These results are similar to reported 100% resistance in one study from India.[12] The reason of high degree resistance even to quinolone and cephalosporins is because of self medication, medication by the pharmacist and quacks in our local community. The injudicious administration and sub-optimal drug dosaging has contributed to the reduced susceptibility and emergence of multi drug resistant S.typhi/paratyphi, not only to the first line drugs but also to the quinolone, azithromycin and cephalosporins. One study from Indonesia revealed 80-90% of typhoid patients were receiving antimicrobials as self medication at home and bed rest; [13] other patients, those with more severe disease and those treated at home who then developed persisting complaints, presented at the health care centers and hospitals.[14] In our study the crucial finding is that the 30% of patients taking antibiotic therapy yielded positive blood cultures in 70% of them, this reveals the existence of drug resistant salmonellae in the community. The self medication and availability of quinolone and 3rd generation cephalosporins without prescriptions is an illegal practice, it must be stopped. It is a challenge for the public health department, which is sleeping this moment.

CONCLUSION

We found drug resistant and multi-drug resistant salmonellae in our study. The usage of quinolone and cephalosporins as self medication, medication by pharmacist and quacks must urgently be prohibited. The public health department must take a strict action to prevent further drug resistant isolates of salmonellae.

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Original Article

Seroprevalence of Toxoplasmosis (By Detecting IgM Antibodies) in Women with Repeated Abortions

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ABSTRACT

Objective: To determine seroprevalence of Toxoplasmosis in women with repeated abortions in our local population.

Study Design: Prospective Cross- sectional study

Place and Duration of Study: This study was conducted in the Department of Microbiology Basic Medical Sciences Institute (BMSI) Jinnah Postgraduate Medical Centre (JPMC) Karachi from April 2006 to May 2008.

Materials and Methods: Sera from 130 pregnant and post-aborted women with history of repeated abortions (group A) and 50 pregnant women with no history of abortion (group B – as controls) were analyzed for Toxoplasma IgM antibodies by ELISA technique to see the prevalence of toxoplasmosis.

Results: 24% of women of group A and 14% of women of group B were seropositive for Toxoplasma IgM antibodies. Most of the cases with toxoplasmosis have had their abortions in the first trimester. Gradual increase in Toxoplasma antibody positivity with increasing gravida was observed.

Conclusion: Women with negative serological status are at risk of acquiring a primary infection during pregnancy, hence education regarding preventive measures should be provided to them and every pregnant woman may be advised for Toxoplasma IgM antibodies investigation.

Keywords: Toxoplasmosis, Repeated abortions, Toxoplasma gondii, ELISA.

INTRODUCTION

Toxoplasmosis, a parasitic and zoonotic disease caused by Toxoplasma gondii[1, 2], is a world-wide health problem[3] affecting mainly pregnant women and their fetuses[4]. This maternal infection with adverse outcome is initially in-apparent and is thus difficult to diagnose on clinical grounds[5, 6.] It is mostly asymptomatic[7], but its clinical implications in pregnant women are manifold. Such patients may have abortions, repeated (two or more than two)[8] abortions, still birth or premature delivery in addition to various foetal anomalies in the form of mental retardation, eye, speech and hearing defects[1,9]. These complications can lead to a significant burden on economic and social structure; hence it would be relevant to determine the prevalence of this infection in local population[10].

According to one estimate over 500 million humans around the world are infected with Toxoplasma gondii. The prevalence of toxoplasmosis is 7% to 51.3% in pregnant women, 17.55% to 52.3% in females with history of abnormal pregnancies and abortions worldwide[2]. In cases of females with history of repeated abortions, the seroprevalence is not similar in different countries like19% in Egypt[11], 49.47% in Srinagar[8] and 53.14% in Indian occupied kasmir[1]. High prevalence of toxoplasmosis was reported in women with repeated abortions in many other studies[12]. Hence, prevalence is different in different countries, even it varies in different parts of the same country[1, 13]. The prevalence also varies in people of different areas of Pakistan. This study was therefore, conducted to determine the prevalence of toxoplasmosis in women with history of repeated abortions.

Today the impact of toxoplasmosis on the health of the unborn child is being discussed worldwide. The availability of sensitive serological methods, the possibility of prenatal diagnosis and treatment of developing foetus are the reasons why World Health Organization (WHO) has encouraged countries to consider the introduction of preventive programmes for pregnant women[14].

MATERIALS AND METHODS

This study was conducted in the Department of Microbiology, Basic Medical Sciences Institute (BMSI) Jinnah Postgraduate Medical Centre (JPMC) Karachi.

130 sera of multi-gravida having 10-20 weeks of gestation and recently aborted females with history of repeated abortions were included as group A in this study. 50 sera of multi-para pregnant females, with same gestational period (10-20 weeks) with no history of abortions, were included as group B.

All the specimens were analyzed for IgM antibodies against Toxoplasma gondii by solid phase indirect Enzyme Linked Immunosorbent Assay (ELISA) technique. All the subjects were selected from the Department of Obstetrics and Gynaecology, JPMC, Karachi. Mostly they were housewives and belonged to

low socio-economic group. The age of these women ranged from 18-45 years. Both groups were matched for age, multi-gravidity and socio-economic status.

The sera were collected aseptically and were separated by centrifuging at 1500 rpm for 10 minutes and were stored in refrigerator at -20°c till tested according to the manufacturer's instructions of commercially available kit [Index Toxo IgM EIA kit by EQUIPAR Diagnostic Saronno (Va), Italy]. The results were read by a microwell-reader compared in a parallel manner with calibrators and controls. Toxo IgM activity index (I.A) of less than 0.90 was taken as negative, 0.91 to 1.10 as equivocal and more than 1.10 was taken as positive for IgM antibodies against Toxoplasma gondii and indicative of a probable current or recent Toxoplasmosis.

RESULTS

Out of 130 sera, from women with repeated abortions (group A), 31 (24%) were found to be positive for Toxoplasma IgM antibody while in controls (group B) 7 out of 50 (14%) were found to be positive (Table-1). Statistically these results were not significant by Chi-square method (P>0.05).

It is observed that most of the positive cases with Toxoplasmosis have had their abortions in the first trimester i.e., 24 out of 31(77.4%) as compared to those second trimester i.e., 7 out of 31 (22.6%) as shown in Table-2. Statistically this highly significant finding indicates that the Toxoplasmosis causes most abortions in the first trimester.

It is also observed that toxoplasma antibodies positivity increases with increase in the number of gravida (Table-3).

Table No.1: Seroprevalence of Toxoplasma IgM antibodies in Women with Repeated abortions (group-A) and Women with no history of abortion (group-B)

Groups	No. of cases tested	Toxoplasma IgM positive		P value
		Total	Percentage	
A	130	31	24%	> 0.05
B	50	07	14%	N.S

N.S= Non-significant

Table No.2: Relationship between Toxoplasmosis and Duration of Pregnancy at which Abortions occurred in repeated abortion cases

Group A (n=130)	First trimester	Second trimester	P value
Toxoplasma IgM positive (n=31)	24 (77.4%)	07 (22.6%)	< 0.01 H.S
Toxoplasma IgM negative (n=99)	42 (42.4%)	57 (57.6%)	

n = Number of subjects
H.S = highly significant

Table No.3: Toxoplasma IgM Positive cases in relation to Number of gravida in group A and B

Group	No. of Gravida	IgM positive cases	Percentage
A (130)*	2-3 (42)*	08	19%
	4-6 (61)*	15	25%
	7-10 (27)*	08	30%
B (50)*	2-3 (23)*	02	09%
	4-6 (24)*	05	21%
	7-10 (03)*	--	--

*Figures mentioned in parentheses are Number of subjects

DISCUSSION

The intracellular protozoan Toxoplasma gondii is a wide spread opportunistic parasite of humans and animals. Normally Toxoplasma gondii establishes itself within brain and skeletal muscles, persisting for life of the host[15]. The domestic cat is the greatest source of human infection[16]. Toxoplasmosis is a primary infection in pregnancy, which can cause foetal infection in 40-50% cases and severe disease in about 10% of babies. It is generally believed that intrauterine transmission of parasites cannot occur in immunological normal female, if she is infected before conception[17]. Transmission of Toxoplasma tachyzoites to the foetus occurs only in mothers who acquire active infection during pregnancy[16]. About one-third of all women infected during pregnancy will transmit the parasite to the feotus. Intrauterine transmission occurs in approximately 15%, 30% and 60% of untreated women who develop acute Toxoplasmosis during first, second and third trimester respectively[1, 2.] Degree of damage depends on the gestational age, since the greatest risk of congenital toxoplasmosis occurs during the first trimester of pregnancy. However, it is during the third trimester that the highest level of transmission occurs but foetal injury is much less severe[18.]

In this study, 24% (31/130) women having a history of repeated abortions were positive for Toxoplasma IgM antibodies while 14% (7/50) women having no history of abortion (as controls) were IgM positive. Although statistically non-significant (P>0.05), these results are rather intermediate when compared with the reported figures in literature, being higher when compared to a study carried out in Egypt by Sahwi and colleagues on 100 cases of repeated abortion, showing 19% of repeated abortion cases and 7.5% of controls seropositive for toxoplasma IgM antibodies[11].In another study in United Arab Emirates (UAE) by Singh, the prevalence was very low and only one case out of 2,343 women of repeated abortion was positive for acute Toxoplasmosis[14]. In this study, prevalence tends to below when compared with two separate studies conducted by Zargar and colleagues in Indian occupied Kashmir where 49.47% and 53.14% were reported in women with repeated abortions[1, 8]. Abdel Hafez from North Jordan reported the presence of anti-Toxoplasma antibodies exceeding two times in habitually aborting women than in non-aborters[19].

The cause of abortions in cases of toxoplasma IgM negative women with history of repeated abortion might be rubella virus, cytomegalovirus, herpes virus, hepatitis virus or others.

In this study, most of the selected cases with toxoplasmosis have had their abortions in the first trimester (24/31) than second trimester (7/31). This highly significant finding indicates that Toxoplasmosis causes more abortions in the first trimester. This is in agreement with Sahwi, who also found most aborted IgM positive cases in the first trimester[11]. It is also found that Toxoplasma positivity increases as the number of gravida increases both in females with history of repeated abortion as well as in control group. This may be due to decreased immunity or increased exposure to organism with increasing age. This is in agreement with Lodhi from Lahore[20] and Ashrafunnessa from Dhaka [21].

CONCLUSION

Our prevalence rate of Toxoplasma IgM antibodies is 24% in women with the history of repeated abortion that is not significant statistically (P>0.05). As our study is restricted to only those patients attending the out-patient department of Obstetrics and Gynaecology , JPMC, Karachi, and the number of subjects is also less as compared to other studies, so a multi-centered study, including large number of subjects and multiple parameters, should be conducted. Women with negative serological status are at risk of acquiring a primary infection during pregnancy, hence education regarding preventive measures should be provided to them. The extent to which Toxoplasmosis causes repeated abortion is still controversial; therefore, a detailed study to correlate Toxoplasmosis with repeated abortions may be done to recommend the mandatory screening of Toxoplasma IgM antibodies in cases of repeated abortion.

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Original Article

A Clincopathological Correlation of Hysterectomies: A Hospital Based Surgical Audit

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ABSTRACT

Objectives: To determine correlation of clinical indication of hysterectomies with histological findings and association with age and parity

Study Design: Institution based cross sectional study

Place and Duration of Study: This study was conducted at the Lady Dufferin Hospital, Karachi, Pakistan from Jan. 2007 to Dec. 2009.

Sample size: 322

Sampling Technique: Non Probability Purposive sampling

Materials and Methods: A structured standardized Proforma was used to collect data between Jan 2007 to Dec 2009 from the pathological laboratory data on surgical hysterectomies. The data comprised of clinical, physical and histological examination. The analysis was made on correlation of clinical indication of hysterectomies with histological findings and association with age and parity.

Main outcome measures: Correlation of Clinical Indications and histological findings on uterus (endometrium and myometrium), cervix and ovaries

Results: Three hundred twenty two abdominal hysterectomies were studied. Among the study subjects the mean $\pm$ SD age was 42.36 $\pm$ 6.36.Only 12 (3.7%) women were unmarried. Clinically the commonest indications were Leiomyoma in 167 (519%) and DUB 120 (37.7%). Ovarian mass was clinical indication in 4 (1.3%) cases. Histopathology revealed leiomyoma 149 (46.3%) as the commonest uterine pathology, followed by adenomyosis. Endometrim showed Chronic endometritis in 22 (6.9%) , hyperplasia in 10 (3.2%) and carcinoma in 2 (0.6%) cases. Inflammation with squamous metaplasia252 (78.2%) was the most common pathology noted in the cervix whereas Squamous Cell Carcinoma was seen in only 1 (0.3%).Most common finding in ovaries was Cystic follicles in 101(46.4%) , cystadenomas were noted in 6 (2.8%) and Benign teratoma in 3 (1.4%).

Conclusions: Hysterectomy is a major gynecological procedure therefore it should be performed after accurate clinical assessment and with proper and justified indications.

Key Words: Correlation, Clinical indication of hysterectomies, histology, Leiomyoma, Andenomyosis

INTRODUCTION

Hysterectomy is one of the most common surgical procedures having a rate of 6.1-8.6/1000 in all ages[1]. There is substantial variation in hysterectomy rates according to geographic, patient related and doctor related factors. Hysterctomy prevalence studies are not available in Pakistan[2].Prevalence of hysterectomy in UK is 100,000/year, 500,000/year in USA and > 70,000/year in England[3].

The first sub-total abdominal hysterectomy with salpingo-oophorectomy was performed by Charles Clay in 1843 and first total in 1929[4].Advances in anesthesia, aseptic techniques and asepsis has brought down the mortality rate of hysterectomies to 0.1%[5].

The most common indications are complains of heavy and irregular uterine bleeding, pelvic pain and pelvic pressure. These symptoms are often associated with uterine leiomyomas, endometriosis, adenomyosis or pelvic organ prolapse. However the same symptoms may occur in the absence of any organic lesions as seen in DUB[5].

The majority of hysterectomies are elective and more than 90 % are performed in women with non malignant conditions. In general hysterectomies are performed to improve the quality of life rather than to cure life threatening conditions. It is the only definitive cure for Abnormal Uterine Bleeding. Multiple studies have shown that symptoms as pelvic pain, dysparunia and fatigue are abolished or significantly reduced after surgery[6].

Hysterectomies may be performed by abdominal or vaginal or a laparoscopic approach. The abdominal or vaginal approaches may be total (involving removal of uterus and cervix) or subtotal (involving removal of uterine fundus and lower uterine segment with preservation of cervix) with or without removal of ovaries[7].

Histopathologically examination has great significance as a diagnosis like adenomyosis can only be established by this procedure. Also DUB which is a major cause of bleeding per vaginum is a diagnosis of exclusion and requires confirmation of absence of any organic lesion. Histopathology is also required for confirmation or to

rule out malignancy in patients with clinical suspicion of malignancy and for their grading and staging[8]. Ultimate diagnosis is only on histopathology so all specimens should be subjected to histopathological examination for a conclusive decision on morphology[9].

MATERIALS AND METHODS

This is a hospital based cross sectional study conducted at Lady Dufferin Hospital, Karachi, during a period of three years from January 2007- December 2009.

This study includes all women undergoing elective abdominal hysterectomy with or without salphingo-oopherectomy.

A short history regarding age parity, presenting signs and symptoms and clinical impressions was recorded on a Proforma and added from hospital records. Specimens were received in 10% formalin solution. Detailed gross examination was done. Appropriate sections were taken processed and stained with routine H & E stain. All slides were examined and reported by consultant histopathologist. Clinical histories with specific focus on age, parity and clinical indications for hysterectomy have been correlated with histological findings. The data was collected and analysed on social package for statistical analysis window version 16.

RESULTS

Three hundred twenty two abdominal hysterectomies were studied. Among the study subjects the mean + SD age was 42.36 + 6.36.Only 40% (14.3%) belonged to parity. 102 (31.7%) females had 4-5 children , closely followed by a group of 95 (29.5%) females who had more than 5 children at the time of hysterectomy. Only 79(32.5%) had 1-3 issues and 46(14.3%) had no children. Only 12 (3.7%) women were unmarried. A past history of early pregnancy loss (spontaneous abortion) was observed in 212 (65.8%) and 3 consecutive abortions in 102 (31.7%) women were observed in the study population.

The order of frequency of complaints among study subjects was: Menorrhagia 121 (37.6%), Polymenorrhoea 63 (19.60), Pain 44 (13.7) and irregular bleeding 43 (13.4%). These characteristics are shown in table I.

Most women 177 (55%) sacrificed both ovaries while one ovary was removed in 41 (12.7%) patients. In 104 (32.3%) both ovaries were conserved and.

The commonest clinical indication was Leiomyoma in 167 (51.9%) and DUB 120 (37.7%) and Andenomyosis was only suspected in 8 (2.5%) women.

Cervical histopathology showed chronic inflammation in 305 (94.7%) cases with additional findings of Squamous mertaplasia in 252 (78.2%). Dysplasia of exocervical squamous epithelium was present in 4 (1.3%) and Squamous Cell Carcinoma was diagnosed in only 1(0.3%) patient.

Uterine myometrium revealed Leiomyoma in 149 (46.3%), Adenomyosis in 102 (31.7%) and Adenomyosis combined with Leiomyoma in 38 (11.8%) patients. No significant pathology was seen in 33(10.2%).

Table No.1: Demographic Characteristics of Hysterectomised Patients n = 322

S #	Characteristics of Hysterectomy Patients	No.	%
1.	Age (Yrs) Mean ± SD 42.36 ± 6.36		
2.	**Marital Status**		
	Married	310	96.3
	Unmarried	12	3.7
3.	**Parity**		
	0	46	14.3
	1-3	79	24.5
	4-5	102	31.7
	> 5	95	29.5
4.	**Previous History of Abortion**	212	65.8
	1-2	102	31.7
	3	8	2.5
	4 & more		
5.	**Major Complaints**		
	Menorrhagia	121	37.6
	Polymenorrhoea	63	19.6
	Pain	44	13.7
	Irregular bleeding	43	13.4
	Pain &	25	7.8
	Menorrhagia	10	3.1
	Postmenopausal	4	1.2
	bleeding	12	3.7
	Primary		
	infertility		
	others		
6.	**Nature of Operation**		
	TAH BSO	177	55
	TAH	104	32.3
	TAH & RSO	41	12.7
7.	**Clinical Diagnosis**		
	Leiomyoma	167	51.9
	DUB	120	37.2
	Adenomyosis	15	4.6
	Endometriosis	12	3.7
	Ovarian mass	4	1.3
	Others	4	1.3

Secretary endometrium 195 (60.7%) was most commonly found and 65 (20.2%) had proliferative phase. In 22 (6.8%) patients endometrial histopathology showed Chronic Endometritis, 8 (2.6%) showed endometrial polyps and10 (3.2%) showed Endometrial hyperplasia. 2 (0.6%) cases of Endometrial Carcinoma were also seen; as in shown in Table 2.

Table No.2: Frequency of Histopathology Reports

1.	**Cervical Pathology**		
	Inflammation and	252	78.2
	metaplasia.	53	16.5
	Inflammation	4	1.3
	Dysplasia	1	0.3
	Carcinoma	12	3.7
	No significant pathology	**322**	**100**
	Total		
2.	**Uterine Muscle Pathology**		
	Leiomyoma	149	46.3
	Andenomyosis	102	31.7
	Leiomyoma+	38	11.8
	Andenomyosis	33	10.2
	No Significant Pathology	**322**	**100**
	Total		
3.	**Endometrial Histopathology**	195	60.7
	Secretary	65	20.2
	Proliferative	10	3.2
	Atrophic	22	6.9
	Endometritis	10	3.2
	Endometrial	8	2.6
	hyperplasia	8	2.6
	Endometrial Polyp	2	0.6
	Disordered Proliferation Endometrial Carcinoma	**322**	**100**
	Total		
4.	**Ovarian Pathology**		
	Cystic follicles	101	46.4
	Corpus luteal cyst	22	10,1
	Endometriosis	17	7.8
	Simple benign cyst	12	5.5
	Cystadenoma	6	2.8
	Benign cystic	3	7.4
	teratoma	1	0.4
	Granlosa cell tumor	1	0.4
	Benign spindle cell	55	25.2
	tumor	**218**	**100**
	No significant pathology		
	Total		
5.	**Fallopian tube pathology**		
	Salpingitis	5	2.3
	Hematosalpinx	3	1.4
	Endometriosis	2	0.9
	No significant	208	95.4
	pathology	**218**	**100**
	Total		

Most common ovarian finding on histopathology was Cystic follicles in 101(46.4%) cases. Endometriosis was seen in 14 (4.3%) patients only. Cystadenoma was seen in 6 (2.8%) whereas Benign Cystic Teratoma was seen in 3 (1.3%) patients.No significant pathology was observed in 55(5.2%) cases.

DISCUSSION

Several complementary approaches are often necessary in the assessment of possible indications for hysterectomy particularly with reference to age and parity among low social group of women[10]. Currently the selection of cases for hysterectomy have been debatable. The major reason is preferred approach for medical and nonsurgical treatment before castration.

The association of clinical findings to histopathology should be helpful for correct decision of surgical approach.

Mean age of study population was 42.36±6.36 in our study which is comparable to previous studies carried out in Pakistan and India. Majority of patients were between 35-45 years of age in the study by Khatoon AB, 2008 and the age is above 40 years in a study by Khawaja N,2005.[11 &12]

The indications most common in this study were leiomyoma (51.9 %), DUB (37.7 %), and ovarian mass(1.3 %). Similar indications were observed to be the most common, in a study by Tahira T in Faisalbad with DUB in 43.3% and leiomyoma in 26.7%[13]. Comparable results are seen in Shergill study in India with leiomyoma (34%) as the most common clinical indication followed by DUB (26%)[14]. Another Nigerian study also reveals leiomyoma (61.8%) to be the most common clinical indication for surgical approach[15]. Chan study also showed comparable percentages for leiomyoma (54.5%) as the most common pre-operative indication [16.] This suggests that uterine leiomyomas and DUB are two major problems requiring hysterectomy.

The association with parity is also significant as currently the trend of indications of hysterectomy starts earlier between 1-3 parity where 24.5% hystrectomies were performed in this study population. Then at parity 4-5,31.7 % and at > 5 parity ,29.5% had hysterectomy. This trend in our study population showed removal of uterus at early parity compared to other populations. This could either be an early decision for surgery before medical treatment, an early clinical diagnosis and an increase in the trend and rate of hysterectomies.

In current study cervical histology showed chronic inflammation in 305 (94.7%) and majority 25 (78,2%) had additional Squamous metaplasia. Zahir N also reported Chronic cervicitis as the most common pathology seen in uterine cervix[17].

Most common pathology of uterine muscle diagnosed on histopathology was leiomyoma 46.3% which correlated with the pre-operative clinical indication very closely. Most common endometrial pathology in our study was endometritis which may have been associated with use of intra-uterine contraceptive devices.

Ovarian pathology was rare clinical indication in our study (1.3%). Histopathology revealed a higher incidence of ovarian pathology in comparison. Cystic lesions were common in ovaries with Cystic follicles detected in 46.4% , cystadenomas in 2.8% and Benign cystic teratoma in 1.4%. Endometriosis was fond in (7.8%) in the current study. Lack of proper prior investigations in our underprivileged and low socio-economic population could be reason for low rate of prior clinical suspicion of ovarian disease.

The bulk of hysterectomised women had major complaints of menorraghia (37.6%), polymenorrahea (19.6%), pain (13.7%) and irregular bleeding 13.4 %. Pain and menorraghia combined were seen in 7.8% cases. These findings suggest that a detailed assessment of history, family history of hysterectomy, physical examination and diagnostic procedures like endovaginal ultrasound, CT Scan, MRI and biomarkers should be requested preoperatively.

Histology with advanced modalities for differentiated tumors or conditions should be recommended. [18,19]

CONCLUSION

Hysterectomy is a major gynecological procedure therefore it should be performed with a proper and justified indications. The gynecological surgeon with a referral note to histopathologist on a structured Performa should request for detail histology. This strategy will provide a better clinicopathological picture of gynecological problem which will be treated and cured completely.

Limitations of study: The study population was from pone private tertiary care hospital and therefore is a unicentre analysis.

Conflict of interest: The authors declared no conflict of interest for this study.

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Original Article

A Comparative Study to Evaluate the Role of Alpha Tocopherol in Pregnancy induced Hypertension

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ABSTRACT

Objective: To assess the role of alpha tocopherol in Pregnancy Induced Hypertension (PIH) by comparing pregnancy induced hypertensive patients on routine anti-hypertensive measures with pregnancy induced hypertensive patients on alpha tocopherol plus routine antihypertensive measures.

Study Design: Retrospective Randomizing Study.

Place and Duration of Study: This study was conducted at the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi from April 2004 to Sept. 2004.

Materials and Methods: Two groups each comprising of 25 pregnancy induced hypertensive females, age ranging from 18-40 years were studied in this study. Changes in systolic and diastolic blood pressure were assessed from 24-28 weeks of pregnancy and were followed at every 15 days till the time of delivery in Control Group-I (G-I) and Test Group-II (G-II).

Results: On day-0 systolic blood pressure on average showed higher value in G-II compared to G-I. On day 30, 60 and day final, the mean systolic blood pressure showed lower values in G-II although the difference was found statistically insignificant. When diastolic blood pressure studied, it showed on the average same readings for G-I and G-II on day-0. On day 30, day 60 and day final, it also showed statistically insignificant difference between G-I and G-II with higher mean diastolic blood pressure in G-I.

Conclusion Alpha tocopherol exerted better effect on systolic and diastolic blood pressure in test group when compared with control group.

Key Words: Pregnancy Induced Hypertension, Alpha Tocopherol.

INTRODUCTION

Pre-eclampsia (PE) remains to be one of the primary causes of maternal and fetal morbidity and mortality all over the world[1]. Pre-eclampsia (PE) and gestational hypertension are the two important conditions mentioned under hypertensive disorders of pregnancy[2]. Gestational hypertension or PIH is the hypertension developing in a female for the first time after 20 weeks of pregnancy[3]. It is defined as systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg. PE is the gestational hypertension plus protienuria whereas eclampsia is the occurrence of seizures in the presence of PE[4]. Pathophysiologically PE is characterized by systemic vascular endothelial dysfunction[5]. For the prevention of PIH (gestational hypertension) antioxidants supplementation is helpful. Antioxidants prevent placental peroxide formation and thus endothelial cell damage is prevented[6]. Supplementation of antioxidants in early pregnancy may decrease oxidative stress, improve vascular endothelial function and ameliorate the course of PE[7]. Antioxidants like vitamin C and E seem to reduce the risk of PE[4].

Therefore, we have designed this study to compare the results of systolic and diastolic blood pressure in Control (G-I) and Test (G-II) groups of pregnancy induced hypertensive patients. Control group was kept on routine antihypertensive measures i.e. lifestyle modifications and antihypertensive drugs as advised by the concerned Obstetrician and Test group was given oral alpha tocopherol in addition to routine antihypertensive measures.

MATERIALS AND METHODS

This study was conducted at the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi in collaboration with Department of Gynecology and Obstetrics Unit II, Ward 9, JPMC Karachi during the year 2004. This comparative study was designed to evaluate the role of alpha tocopherol in pregnancy induced hypertension.

Study groups; Group-I (control group) comprised of 25 pregnancy induced hypertensive females ages ranging from 18 to 40 years. They were enrolled during 24-28 weeks of pregnancy at Day-0. They were kept on routine antihypertensive measures and were

evaluated at every 15 days till the end of pregnancy (day of final reading) for changes in systolic blood pressure and diastolic blood pressure.

Group-2 (Test group) comprised of 25 pregnancy induced hypertensive females age 18 to 40 years. They were enrolled during 24-28 weeks of pregnancy at day-0. They were kept on routine antihypertensive measures plus capsule alpha tocopherol 400 I.U per day and were evaluated at every 15 days till the end of pregnancy (Day of final reading) for changes in systolic blood pressure and diastolic blood pressure.

Written consent was taken from all the participants before they were enrolled in study. Exclusion criteria for both groups were diabetes mellitus, any evidence of liver disease, renal disease or twin pregnancy and patients who were using aspirin therapy.

Blood pressure was measured by standard mercury sphygmomanometer. The results were evaluated by paired *t* test, student *t* test and percentage.

OBSERVATIONS AND RESULTS

The observations of both groups-I and II were evaluated on day 0 i.e. at 24-28 weeks of gestation, day 30 i.e. 28-32 weeks, day 60 i.e. 32-36 weeks and at day of final reading (DF) which was ≥ 36 weeks of gestation.

Table No.1: Comparison of mean Systolic Blood Pressure (mmHg) in patients with Pregnancy Induced Hypertension (PIH) (group-i) with Pregnancy Induced Hypertension (PIH) taking Alpha Tocopherol Group-II of different gestational age ranges from 24-36 weeks, recorded from day- 0 to day-final.

Mean Systolic Blood Pressure (mmHg) in different Gestational age ranges from 24-36 weeks					*P* Value				% age Change
Groups	**At Day-0 24-28 Week**	**At Day-30 28-32 Weeks**	**At Day-60 32-36 Weeks**	**At D. F ≥36 Weeks**	**D0-D30**	**D30-D60**	**D60-DF**	**D0-DF**	**D0-DF**
G -I (n=25)	132.4±1.05	127.6±1.76	127.6±2.26	130.8±2.51	<0.001	N.S	N.S	N.S	↓ 1.20%
G - 2 (n=25)	134±1	125.2±1.43	127.2±1.98	129.2±2.23	<0.001	N.S	N.S	<0.01	↓ 3.50%

Key: G-I = Control Group DF = Day of final reading N.S = Non Significant
G-2 = Test Group Figures in Parentheses indicate number of patients

Table No.2: Comparison of Mean Diastolic Blood Pressure (mmHg) in Patients with Pregnancy Induced Hypertension (PIH) (Group-I) with Pregnancy Induced Hypertension (PIH) taking Alpha Tocopherol (Group-II) of different Gestational age ranges from 24-36 weeks, recorded from day 0 To day final.

Mean Diastolic Blood Pressure (mmHg) in different gestational age ranges from 24-36 weeks					*P* Value				%age Change
Groups	**At Day-0 24-28 Weeks**	**At Day-30 28-32 Weeks**	**At Day-60 32-36 Weeks**	**At D.F. ≥36 Weeks**	**D0-D30**	**D30-D60**	**D60-DF**	**D0-DF**	**D0-DF**
G -I (n=25)	91.6±0.75	86.4±1.28	87.6±1.85	88±1.63	<0.001	N.S	N.S	<0.01	↓ 3.9%
G -2 (n=25)	91.6±0.75	84.4±1.17	85±1.41	87.6±1.85	<0.001	N.S	N.S	<0.01	↓ 4.3%

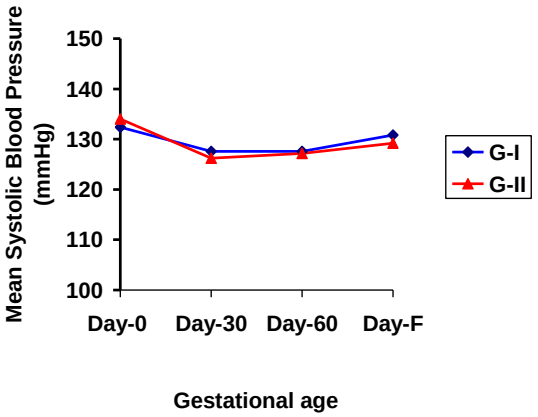
Key: G-I = Control Group D.F = Day of final reading N.S=Non Significant
G-II = Test Group Figures in parentheses indicate number of patients

Systolic Blood Pressure

Control group-I: All the 25 enrolled pregnancy induced hypertensive patients were studied till the day of final reading. Mean systolic blood pressure as shown in **Table-1** and **Figure-1** was decreased from 132.4±1.05 mm Hg on day-0 to 127.6±1.76 mm Hg on day-30, the decrease was found statistically highly significant, it remained same on day-60 and increased to 130.8± 2.51 mm Hg on the day of final reading. The reduction in systolic blood pressure was statistically highly significant from day 0 to day 30. Whereas, insignificant results were obtained when this reduction was compared from day 30-60 and rise in systolic B.P compared from day 60 to day of final reading. The decrease in systolic blood pressure from Day-0 to Day of final reading was statistically insignificant. The change in systolic blood pressure was found to be 1.2% reduction from day-0 to day of final reading.

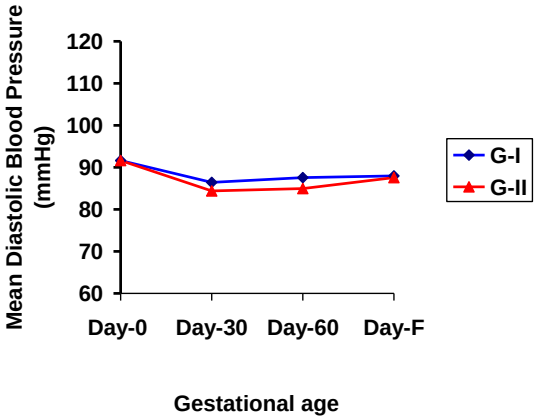
Test group –II: In this group 25 enrolled pregnancy induced hypertensive patients were studied from day-0 to day of final reading. The mean systolic blood pressure as shown in **Table-I** and **Figure-I** was

decreased from 134±1.0 mm Hg to 125.2±1.43 mm Hg from day 0 to day-30 that showed highly significant decrease ($p<0.001$). Then systolic blood pressure was increased to 127.2±1.98 mm Hg on day-60 and again it increased to 129.2±2.23 mm Hg on day final, both of these changes were found statistically insignificant. Whereas, the decrease in blood pressure from day-0 to day final reading was statistically significant ($p<0.01$) and it was reduced by 3.5 %.



Key: G-I=Control Group, G-II=Test Group
Day-F=Day-Final reading

Figure No.I: Changes in Mean Systolic Blood Pressure(mmHg) in different gestational age ranges from 24-36 weeks recorded from Day-0 to Day Final of patients Group-I (G-I) & Group-II(G-II)



Key: G-I=Control Group, G-II=Test Group
Day-F=Day-Final reading

Figure No.2: Changes in Mean Diastolic Blood Pressure(mmHg) in different gestational age ranges from 24-36 weeks recorded from Day-0 to Day final of patients Group-I (G-I) & Group-II (G-II)

Diastolic Blood Pressure

Control group-I: The mean diastolic blood pressure as shown in **Table-2** and **Figure-II** was decreased from 91.6±0.75 mm Hg on day-0 to 86.4±1.28 mm Hg on day-30 with highly significant reduction ($p<0.001$). Whereas, an increase was observed 87.6 ±1.85 mm Hg on day-60 which was further increased to 88±1.63 mmHg on day of final reading but both results were found to be statistically non-significant. The decrease in diastolic blood pressure from day-0 to day of final reading was found statistically significant (3.9%).

Test group-II: The mean diastolic blood pressure as shown in **Table-2** and **Figure-II** on day-0 was 91.6 ±0.75 mm Hg and it significantly decreased to 84.4±1.17 mm Hg on day-30 ($p<0.001$). It was also increased to 85±1.41 mm Hg on day-60 and it again increased to 87.6±1.85 mm Hg on day of final reading; however, both changes were found statistically non-significant. The decrease in mean diastolic blood pressure from day-0 to day of final reading was noted statistically significant($p<0.01$)with a decrease of 4.3%.

Comparison of Change in Blood Pressure

Systolic Blood Pressure

G-I vs. G-II: On day-0, the difference in systolic blood pressure on the average showed slightly higher value in G-II, however, when tested statistically the difference was found non-significant between G-I and G-II. On day-30, 60 and day final the mean systolic blood pressure on the average showed lower values in G-II, and the difference was found insignificant statistically. The change in mean systolic blood pressure from day-0 to day final in G-I was found less decreasing i.e. (-1.2%) as compared to G-II (-3.5%).

Diastolic blood pressure

G-I vs. G-II: On day-0, diastolic blood pressure on the average has shown same readings for G-I and G-II. On day-30, day-60 and day final the results showed statistically non-significant differences between G-I and G-II with higher mean diastolic blood pressure in G-I. The change in mean diastolic blood pressure from day-0 to day final reading in G-I was less decreasing (-3.9%) as compared to G-II (4.3%).

DISCUSSION

A large number of studies have shown that gestational hypertension or pregnancy induced hypertension (PIH) and pre-eclampsia can result in substantial infant and maternal mortality worldwide. Regarding PE, vascular endothelial damage is the basic pathophysiological mechanism. Free radical mediated lipid peroxidation may be involved in this endothelial damage[8]. Free radicals i.e., Reactive Oxygen Species (ROS) may produce a state of oxidative stress. Oxidative stress develops when reactive oxygen species level exceeds the scavenger capacity by antioxidants. Anti-oxidants like vitamin E and C can disperse, remove or decrease the formation of (ROS)[9].

In view of the importance of PIH and PE that can lead to eclampsia in developing countries like

Pakistan. we have conducted a comparative study to evaluate the role of alpha tocopherol in pregnancy induced hypertension. In our study Group-2 patients were compared with Group-1 patients for changes in systolic and diastolic blood pressure. The fall in systolic and diastolic blood pressure in our study at the end of pregnancy i.e. on the day of final reading was more in G-II as compared to G-I but the difference was found statistically insignificant.

The study of Shennan *et al*[10] and Chappell *et al*[7] targeted preeclampsia by keeping their patients on the prophylactic treatment, they had supplemented with vitamin C 1000 mg and vitamin E 400 I.U in women who were at higher risk of PE from second trimester of pregnancy. They have evaluated that there was at least 50% reduction in the development of PE by this supplementation. Their findings are in correlation with the results of our study in which we have also found comparatively better effects in treated group.

According to study results of Duley et al 1996, the risk of preeclampsia can be reduced by using antioxidant therapy. Whereas, the study of Chappel et al in 1999 has compared early supplementation of vitamins E and vitamin C with placebo in women with increased risk of PE from 16-22 weeks of pregnancy and continued throughout pregnancy, his results match with our results, there was a significant reduction in systolic or diastolic blood pressure in the proportion of women with PE who had received vitamin therapy.

CONCLUSION

The results of this study show that a better control on systolic and diastolic blood pressure in pregnancy induced hypertensive patients that was observed when alpha tocopherol was administered orally along with anti-hypertensive measures. Future studies need to be carried out on various parameters and on larger scale to confirm the role of alpha tocopherol as antioxidant in controlling pregnancy induced hypertension and pre-eclampsia.

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Original Article

Early Results of Ponseti Technique for Idiopathic Congenital Talipes Equinovarus

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ABSTRACT

Clubfoot or congenital talipes equinovarus is one of the most common congenital anomaly affecting the lower limb. The exact cause is unknown and a number of theories have been postulated to explain its origin. Congenital talipes equinovarus affects both sexes and may be unilateral or bilateral. Clubfoot is sometimes associated with Arthrogryposis multiplex congenita, spina bifida, meningomyelocele and muscular dystrophies.

Objective: This study was conducted to determine the early results of ponseti technique for idiopathic congenital talipes equinovarus.

Study Design: Observational (Follow-up) Study.

Place and Duration of Study: This study was conducted at orthopedic B-Unit of Ayub Teaching Hospital Abbottabad from 1st April 2009 to 30th September 2009.

Materials and Methods: Thirty (30) patients from either gender with age from birth to 06 months of age attending the outpatient department of Orthopedic B-Unit of Ayub Teaching Hospital Abbottabad were included in the study.

Results: The patients were ranged in age from birth to o6 months of age, with 17 male (56.7%) and 13 female (43.3%). In our series on follow up, fore foot adduction was detected in 06 cases (20%) and 02 cases had equinus relapse (6.7%) and 03 patients had residual equinus (10%) while bilateral residual equinus was detected in 01 patient (3.3%) and 01 patient had recurrence of deformity (3.3%) for which posteromedial release was done.

Conclusion: We concluded that the Ponseti method is a reliable, simple, effective and safe method for the treatment of idiopathic clubfoot deformity.

Key Words: Clubfoot, Ponseti casting, results, Talipes equino varus, CTEV

INTRODUCTION

Congenital tallipes equinovarus is one of the most common human congenital malformations[1]. Its incidence is approximately 01 in every 1000 live births[2]. The word tallipes means talus (ankle), pes (foot). The word clubfoot denotes the club like appearance of foot, where the patient walks on outer aspect of talus.CTEV describes the end results of untreated deformity of foot.CTEV is hereditary foot deformity of unproven etiology, which affects both sexes, but males more frequently than females. The condition may be unilateral or bilateral. It is often associated with other conditions such as Arthrogryposis multiplex congenita, spina bifida, meningomyelocele and muscular dystrophies[3].

. There is an increased incidence in certain racial and ethnic groups with much higher incidence if the patient has a positive family history of clubfoot.

CTEV has following components[4]:

1. Equinus; the forefoot is dropped planter wards at ankle and heel cord is tight. At mid tarsal level planter structures are tight.
2. Varus of the heel; It is due to the tight medially inserted heel cord and medially contracted ligaments which resist correction.
3. Adduction or varus of forefoot.
4. Supination; It is rotation about the longitudinal axis of foot with elevation of medial boarder.

The anterior and posterior tibial muscles pull the first metatarsal and navicular in to inversion. In addition the contracted planter aponeurosis and muscles create the cavus deformity. The anterior end of talus forms the dorsal and lateral bony deformities. In addition abnormal skin creases of foot and calf muscle atrophy may also be present. Mid foot & fore foot are adducted & inverted. Foot & leg have a golf club stick like appearance.

The severity of deformity in clubfoot can be assessed by various methods but a number of criteria one of which is Pirani scoring system. The pirani scoring system, together with the ponseti method of clubfoot management, is reliable, quick and easy to use method for clinical assessment of an Individual clubfoot[5].

The pirani score comprises six clinical signs, three in midfoot and three in hind foot. The amount of deformity is graded between 0 and 3. The score 0 is for normal, score 0.5 is for moderately abnormal and score 1 shows severe abnormality. The three signs that comprise midfoot score are (1) Curved lateral boarder (2) Medial crease (3) Talar head coverage. The three signs that comprise the hind foot score are (1) Posterior crease (2) Rigid equinus (3) Empty heel.

The importance of clubfoot and its conservative management has increased in past recent years.

Regarding treatment most of the authors agree that the appropriate initial management for all children with clubfoot is non operative[6]. Ponseti technique is a well proven way of managing clubfoot deformity[7]. Ponseti method has been shown to be affective in children up to two years of age[8]. The key principles of this method are

1. All deformity components are corrected simultaneously except equinus, which is corrected at last usually by percutaneous Achilles tenotomy.
2. Correction is maintained by external foot rotation around the head of talus.
3. Extra cavus is corrected by supination of the first ray of foot.
4. The corrections are performed weekly and plaster cast is applied.

After 04 to 05 weeks of treatment, a percutaneous Achilles tenotomy is performed under local or general anesthesia.. After another 03 weeks of immobilization in a plaster cast, the feet are given an abduction brace, worn continuously for three months and then at night for 02 to 04 yrs.9.

Clubfoot results in severe handicap unless managed early (Fig 1). Untreated patients not only develop progressive increase in deformity associated with late adoptive changes, but also result in poor function and cosmetic even after surgical correction.

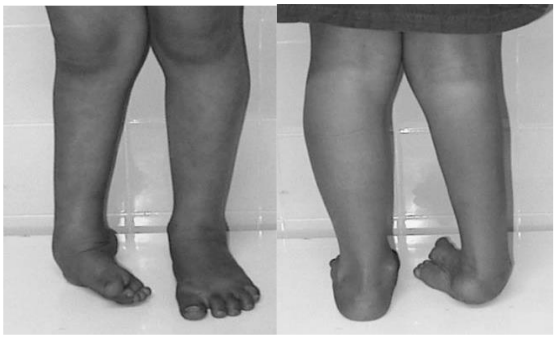


Figure No.1: Photographs of an eight-year old girl with a) right neglected club foot with atrophy of the calf muscles and severe deformity with weight bearing on the lateral aspect of the foot causing thickening of the skin and bursitis, b) severe varus of the heel and supination of the foot

MATERIALS AND METHODS

This follow-up study was conducted at OPD in orthopedic unit of Ayub Teaching Hospital, Abbotabad from April 2009 to September 2009. Thirty consecutive patients of age from birth six months were enrolled in this study. Previously operated cases or patients Clubfoot associated with other congenital anomalies like Arthrogryposis multiplex congenital, Meningomyelocele and Spina bifida were not included in study.

Initial Assessment:

All the patients attending the outpatient department of the orthopedic unit with idiopathic congenital tallipes equinovarus meeting inclusion and exclusion criteria were included in study. An informed consent was taken from the patient's parents or attendants. Detailed patient history especially about the family history and parent marriage (cousin or non relative) were asked. A detailed clinical examination was performed, starting from feet for cavus, heel varus, fore foot adduction and equinus of hind foot. Movements of the ankle, knee joint and hip joint of both limbs were also assessed. In addition the spine and the head were also examined. The deformity was classified according to Pirani scoring system.

Ponseti Management:

Patients of idiopathic congenital clubfoot were taken to plaster room along with their parents or attendants. The patients were put in a spine position on a comfortable couch. All the necessary arrangements were made for application of plaster cast, such as arrangement of cotton roll and plaster of Paris and a bowel full of water. The child was allowed to feed before and during the application of POP casts.

A thorough examination of the feet was done. The degree of severity was assessed according to pirani system and all the findings were noted down on the preformed. After that the diseased foot was manipulated for 60 seconds in desired position according to the number of cast, i.e. supination position for the first cast and abduction for second to fourth casts and abduction and dorsiflexion for fifth (post tenotomy) cast.

After manipulation for 60 seconds, an assistant was holding the foot in position for application of plaster cast while surgeon was applying the cast. The cast was applied from foot to mid thigh (above knee) of the involved foot at once in small children. The cast was applied in two steps in some patients with big legs and feet, first from foot to below knee and then from below knee to mid thigh above. In every cast care was taken to keep the knee joint in flexion from 10 degrees to 15 degrees. The foot was held in a desired position for that particular cast until the wet plaster cast gets dry and hardened and holds the foot in that particular position.

After that the fingers of the foot on which the plaster cast was applied were cleaned with a water socked cotton swab and the fingers were checked for any discoloration or swelling. The parents were allowed to take their child and sit on a chair nearby for 10 minutes, during which time they were told to feed the child.

After 10 minutes, the fingers of the foot on which the plaster cast was applied was checked again for discoloration, congestion and swelling. In a very few cases, there was congestion and swelling after the application of plaster cast, for which the cast was removed and a new cast was applied to that foot in a

very careful manner avoiding any tightness in the course of the POP cast.

If there was involvement of the other foot as well, the whole process of manipulation and application of plaster cast was repeated.

Post Casting Management

After the application of POP cast, the child and the parents were told to wait for at least 10 minutes to check for any discoloration or swelling of the foot. If found satisfactory then the patient was allowed to go home with instructions regarding the care of the plaster cast and about complications of the plaster cast. The parents were educated regarding how to check the foot for complications of the plaster cast. The parents were instructed that if they find or suspect any complication, they must take the child back to hospital or nearby health facility as soon as possible. In addition, they were also given the contact number of the surgeon so that parents can take advice from the surgeon at any time.

First follow up visit was after two weeks to troubleshoot compliance issues. The subsequent follow up visits were at third month and then sixth month for assessing the correction or recurrence of a part or whole of the deformity.

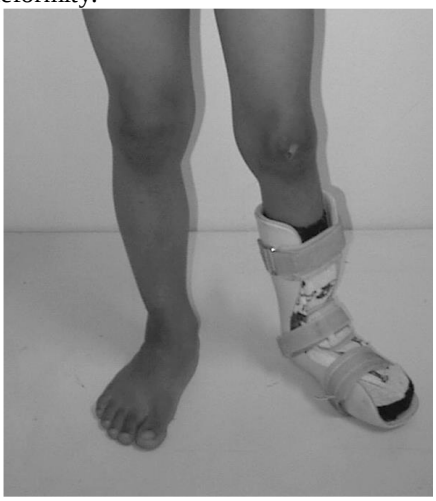


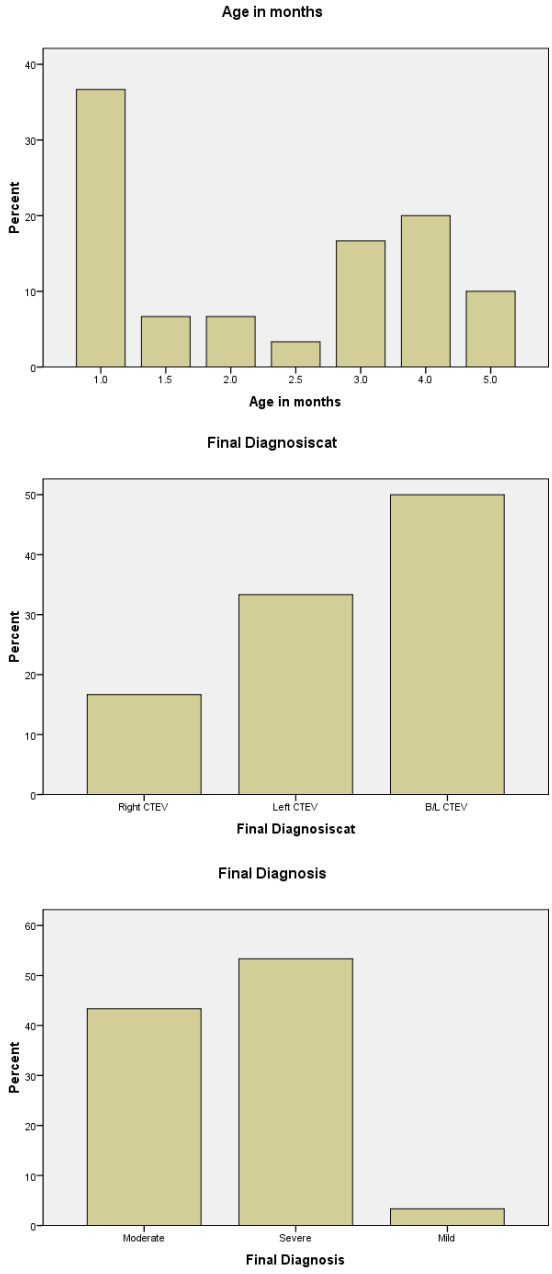
Figure No.2. Photograph showing the ankle foot orthosis used to maintain correction.

Data Analysis Procedure:

The collected data was entered and analyzed accordingly using SPSS version 11 through its statistical program. The study variables were age, sex, affected extremity, mode of injury and functional outcome. The continuous variables were expressed as Mean ± SD, whereas the categorical variables in the form of frequency and proportion.

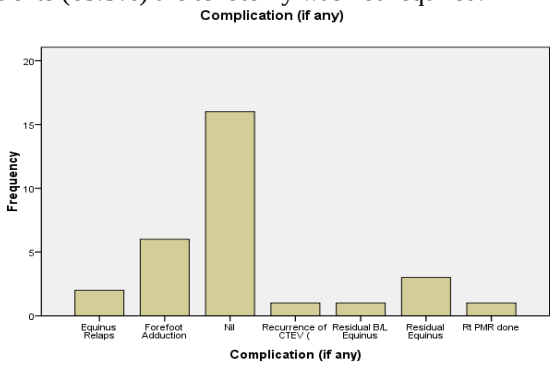
RESULTS

The patients were ranged in age from birth to o6 months of age, with 17 male (56.7%) and 13 female (43.3%). There were total 05 patients presenting with right C.T.E.V (16.7%), out of which 01 was male and the rest of four were female. There were total 10 patients presenting with left C.T.E.V (33.3%), out of which 07 were male and 03 were female. Bilateral C.T.E.V was present in 15 patients (50%), out of which 09 were male and the rest of the 06 were female. There was 01 patient with mild C.T.E.V (3.3%), while 13 patients had moderate C.T.E.V (43.3%) and the rest of 16 patients had severe C.T.E.V (53.3%).



The family history of C.T.E.V was positive in 10 patients with 08 patients have history of C.T.E.V in their cousins (26.6%) and 02 patients having history of C.T.E.V in their other relatives (6.7%). There were 20 patients (66.7%) having history of parent marriage between cousins, which means that both the parents

were cousins, while the parents of the rest of the 10 patients (33.3%) were not relatives. There were 20 patients (66.7%) who had no history of casting before starting ponseti treatment while the rest of the 10 (33.3%) had history of casts applied by other doctors. There were 11 patients (36.7%)in whom Achilles tenotomy was performed while in the rest of the 19 patients (63.3%) the tenotomy was not required.



In our series on follow up, fore foot adduction was detected in 06 cases(20%) and 02 cases had equinus relapse (6.7%) and 03 patients had residual equinus (10%) while bilateral residual equinus was detected in 01 patient (3.3%) and 01 patient had recurrence of deformity (3.3%) for which posteromedial release was done.

DISCUSSION

The method of serial manipulations and casting developed and mastered by Ignacio Ponseti at the University of Lowa in 1950 was instituted and applied to infants with congenital clubfoot in an effort to achieve a plantigrade, functional and a cosmetically acceptable foot without surgical intervention.

Since the early 1970s, there was a trend toward the surgical intervention in cases of congenital talipes equinovarus, primarily in the form of the posterior and medial soft tissue releases as described by Turco with modifications by Crawford et al and McKay[104]. However, extensive surgical release carries both immediate and long term inherent risks for example wound complications including infection, scarring, dehiscence, and neurovascular compromise may occur in immediate setting. Long term complications includes the overcorrection with calcaneus deformity, heel valgus, pes planus, forefoot abduction and under correction with persistent equinus, heel varus and metatarsus adductus may also occur. Because these complications become more readily evident, a renewed interested in non surgical treatment of C.T.E.V has occurred. This renewed interest has focused attention on the Ponseti method because of the previously reported high rates of success.

The goal of this research is to show the early results of ponseti technique for idiopathic club foot. We have been trying to define and correct therapeutic guidelines thereof in order to obtain patients better functional status (Fig 2) and, consequently, their better quality of life and work capability in future. The sample was homogenous in respect to the sex-age distribution, which minimizes the probability of making a statistical mistake.

In our study, there were with 17 male (56.7%) and 13 female (43.3%). There were total 05 patients presenting with right C.T.E.V (16.7%). There were total 10 patients presenting with left C.T.E.V (33.3%). Bilateral C.T.E.V was present in 15 patients (50%), out of which 09 were male and the rest of the 06 were female. There was 01 patient with mild C.T.E.V (3.3%), while 13 patients had moderate C.T.E.V (43.3%) and the rest of 16 patients had severe C.T.E.V (53.3%).

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In a study conducted by Michael and Matthew, 95% club feet were corrected without requiring PMR, while in our study 96.7% were corrected without requiring a posteromedial release[105]. In their study 28% were corrected with manipulation and casting alone while in our study 63.3% was corrected without requiring tenotomy. In their study only 5% required a posteromedial release while in our study only 3.3% required posteromedial release. In their study 67% of the clubfeet were corrected with serial manipulations and casting and with Achilles tenotomy while in our study tenotomy was performed in 36.7% of cases along with serial manipulations and casting. In their study 6 cases suffered a relapse despite initial successful correction, while in our study only 1 case suffered relapse of clubfoot deformity which favors our study. However in that case the parents admitted to noncompliance with the foot abduction brace regimen.

Limitations of this study include the relatively small number of patients and short follow up. In children who received previous casts, we were unable to verify

precisely what type of casting or treatment they received, and whether this treatment corrected any of their initial deformity or created an additional pathology. Most of the children took their children to traditional bone setters and only those consulted the hospital in which the deformity was severe.
However, a longer follow up study will show the functional outcomes of clubfeet treated by this method.

CONCLUSION

We concluded that the Ponseti method is a reliable, simple, effective and safe method for the treatment of idiopathic clubfoot deformity. On one hand, this treatment protocols leads to a reliable restoration of the clubfoot deformity to a functional, plantigrade and cosmetically acceptable foot in majority of our patient series. In most of cases, the need for posteromedial release was obviated and potential complications of the surgical procedures were avoided. On the other hand, timely treatment and an adequate therapeutic method can significantly reduce the risk of secondary and final complications and bring to satisfying quality of life and work capability

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Original Article

Incidence of Liver Cirrhosis in Infancy and Childhood

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ABSTRACT

Cirrohsis is the end result of chronic liver disease caused by the different pathological factors including congenital malformation, inflammation (hepatitis) and metabolic / storage disorders, leading to liver cell damage. To determine the incidence of liver cirrhosis in infancy and childhood with chronic hepatitis, we studied 41 biopsies of children for the presence of cirrhosis.

Objectives: To provide an overview of current childhood statistics of hepatitis and liver cirrhosis to facilitate analysis of the impact of past research discoveries on outcome and provide essential information for prioritizing future research directions.

Study Design: Retrospective Study.

Place and Duration of Study: This study was conducted at the Department of Basic Medical Sciences Institute, JPMC, Karachi from Jan. 2000 to Dec. 2007.

Materials and Methods: Slides / paraffin blocks of liver biopsies from patients under 15 years of age. The cases were of two categories i.e. retrospective & prospective. The distribution of 41 cases of hepatitis was according to Age & Sex. Total 22 (53.7%) cases were encountered in the youngest of 0-5 years age group, 13 (13.7%) cases in 6-10 years and only 6 (14.6%) cases in 11-15 years age group.

Results: The distribution of 41 cases of cirrhosis of liver, according to age & sex . the maximum 22 (53.77 %) youngest case in 0-5 years ,13 (31.7%) cases in 6-10 years & 6 (14.6%) cases were found in 11-15 year age group.

Conclusion: It is observed that the tendency of liver inflammation was decreased with increasing age and sexual differentiation shows male predominance with male to female ratio of 2.4:1. Liver cirrhosis discovered with increasing age in children. It is found to be a common cause for enlargement of liver with associated hepatitis and chronic liver diseases in infants and children. It can lead to higher risks of acute or chronic responses in adulthood and will require new treatment paradigms building on an increased understanding of the molecular processes for infancy and childhood liver cirrhosis.

Key Words: micro nodular cirrhosis, macro nodular cirrhosis, mixed type of cirrhosis, biliary cirrhosis.

INTRODUCTION

Liver Cirrhosis is a common disease[1]. Fibrotic nodules formation in liver are associated with ascites, occurred frequently[2]. In the presence of jaundice many cirrhotic livers appeared green in color instead of brown. The tawny color is due to a deposition of iron in the cirrhotic tissue. In the course of any liver inflammation, Cirrhosis can develop[3]. It has been customary to classify Cirrhosis in accordance with gross anatomic alterations[4] occurred in Portal Cirrhosis and Biliary Cirrhosis[5].

Cirrhosis is the end result of chronic liver disease, like congenital malformation, inflammation (hepatitis) and metabolic / storage disorders leading liver cell damage. Hepatic infection has become a major worldwide health problem due to potential natural course of the disease leading cirrhosis and then hepatocellular carcinoma[6,7]. In chronic liver diseases, the regeneration of liver cells are partial and gradual with impairments of functions. Due to increased fibrosis normal lobulation of liver is lost and there is pseudolobules formation is taken place as cirrhosis. In focal and minor injuries the complete regeneration may be possible[8]. Liver cirrohsis is the end result of protected liver damage[9]. Cirrhosis appears in compensated or decompensated state, in childhood compensated state of cirrhosis is compatible with normal growth and development for prolonged periods. An extensive list of causes is outlined in (Table 1)[18]. Researches demonstrate by sequential biopsy the progression from neonatal hepatitis to cirrhosis in a young child.

In Karachi, liver cirrhosis rate is increasing day by day. About 70% of the all new born have transplacental IgG antibodies against hepatitis[10] that last about 8 months of age. Due to lack of proper health facilities or poor economical status and less public awareness about the transmission of major communicable diseases like hepatitis B, hepatitis C and Human Immunodeficiency syndrome causing the increase in cases of cirrhosis[11].

MATERIALS AND METHODS

Slides / paraffin blocks of liver biopsies from patients under 15 years of age. the cases were of two categories i.e. retrospective & prospective.

Retrospective:

1. Slides / paraffin blocks of liver biopsies received during last 10 years in the Department of

Pathology, Basic Medical Science Institute (BMSI), Jinnah Postgraduate Medical Center, Karachi.

2. Slides / paraffin blocks of liver biopsies received in Department of Pathology, National Institute of Child Health (NICH) Karachi during last 7 years.

Prospective: Slides / paraffin blocks of liver biopsies received during last 10 years in the Department of Pathology, Basic Medical Science Institute (BMSI), Jinnah Postgraduate Medical Center and National Institute of Child Health (NICH) Karachi. A clinical protocol including the particulars about the patients name, age , sex and diagnosis were obtained from the surgical pathology registers, request cards and copies of report.

RESULT

The distribution of 41 cases of cirrhosis of liver, according to age & sex . the maximum 22 (53.77 %) youngest case in 0-5 years ,13 (31.7%) cases in 6-10 years & 6 (14.6%) cases were found in 11-15 year age group.

Table No.1: Showing causes of Liver Cirrhosis

Presenting in Infancy Viral	Presenting in Childhood
Cytomegalovinus	**Infectious**
Rubella	Chronic Hepatitis B+ _ delta
Herpes simplex	Chronic Hepatitis C
Hepatitis B	**Metabolic/genetic**
Delta Hepatitis	Alpha-I-antitrypain
Bacterial	deficiency
Syphilis	Cystic fibrosis
Metabolic/Genetic	Wilson disease
Alpha-Lantitypsin deficiency	Indian childhood cirrhosis
Galactosemia	Hepatic porphyria
Fruclosemia	**Hepatobiliary anatomic**
Tyrosinosia	Choledochal cyst
Glycogen storage disease type 3,4	Intrahepatic cystic biliary
Niemann-Pick disease	Dilation (Caroli disease)
Wolman disease	Congenital hepatic fibrosis
Idiopathic	Sclerosing cholangitis
Neonatal hepatitis	**Toxic/drug**
Familial intrahepatic cholestasis	Malnutrition
Biliary trec abnormalities	Hepatotoxic drug
Extrahepatic biliary atresia	
Arteriohepatic dysplasia	
Intrahepatic duct paucity	
Choledochal cyst	
Vascular	
Congestive cardiac failure	
Constrictive paricarditis	
Veno-occlusive disease	
Budd-Chiari syndrome	
Toxic	
Parenteral nutrition	

Table No.2: Showing age and sex Differentiation in Young Population

Age	Male	%	Female	%	Total	%
0-5	16	55..8	6	50.0	22	53.7
6-10	7	24.1	6	50.0	13	31.7
11-15	6	20.1	O	0	6	14.6
Total	29	100	12	100	41	100

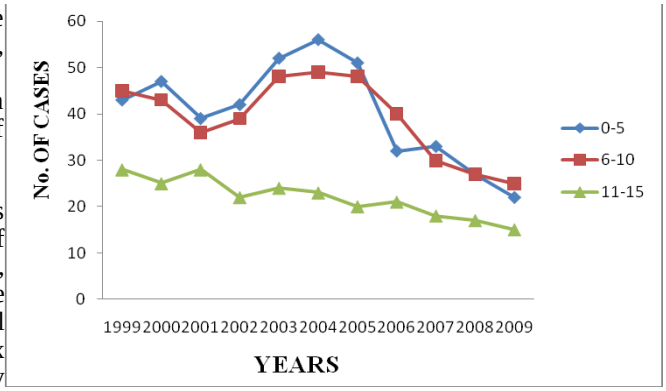

Figure 1: Showing year wise distribution of 41 cases reported for Physiological Liver Cirrhosis and Hepatitis

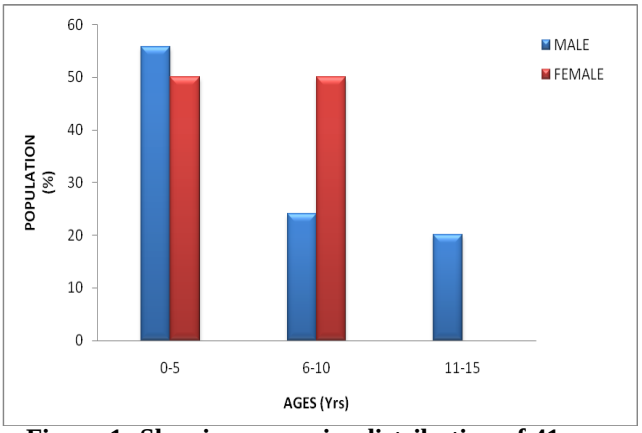

Figure 1: Showing year wise distribution of 41 cases reported for Physiological Jaundice and Hepatitis

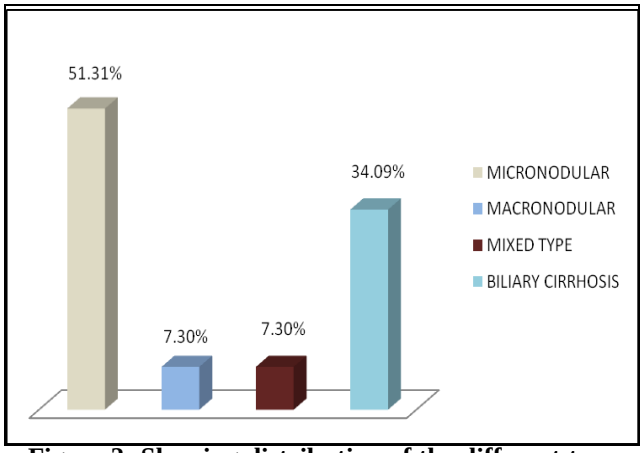

Figure 2: Showing distribution of the different types of Liver Cirrhosis in 41 cases

DISCUSSION

Hepatitis is associated with the necrosis of liver cells with fibrosis and is a major cause of liver diseases[12,13]. Severity of inflammation and necrosis with parenchymal fibrosis was published in Hepatology as histology activity index (HAI) in 1981[14]. Chronic persistent hepatitis has a generally good prognosis as

compare to Chronic aggressive hepatitis which can cause liver cirrhosis[15]. This may lead to portal hyper tension and liver failure. The primary causes of cirrhosis of the liver in infants and children in many parts of the world are hepatitis and congenital malformation of the biliary tree[16]. There are various types of liver cirrhosis reported in children (Fig.2) in which most of the cases were of macronodular type. This type of cirrhosis can occur after any disease that causes liver cell death. Exactly why the regenerating nodules are not able to replace the function of the liver is not clear, although it may be the scarring itself that prevents the functional recovery. The disease is not entirely benign in children, more clinical cases are being diagnosed due to the increased age of those susceptible, which is paradoxical to childhood infection where the majority of infections are subclinical[17].

CONCLUSION

There was over all decrease in tendency of the disease with increased age & male to female ratio was 2.4:1, with male predominance. Our results indicate that the incidence of cirrhosis is high in children with chronic hepatitis, especially of the autoimmune type, and that cirrhosis may occur early, irrespective of cause.

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Original Article

Effects of L-Arginine on Fatty Diet Induced Changes in Adrenal Cortex: A Morphometric Study

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ABSTRACT

Aim: To study the effects of L-Arginine on high fat diet induced changes in adrenal cortex.
Study Design: A prospective experimental study.
Place and Duration of Study: This Study was conducted at the Department of Anatomy, Basic Medical Sciences Institute, Jinnah Post Graduate Medical Centre Karachi from August 2008 to October 2008.
Materials and Methods: Thirty male adult albino rats were taken for the study and were divided into three groups according to the dietary regimen. Group A received control diet. Group B received high fat diet with 20% added fat in the form of butter. Group C received high fat diet along with L-Arginine 300mg/kg / day orally. After the end of the study period that is 8 weeks, animals were weighed and sacrificed. The adrenal glands were removed, fixed in buffered neutral formalin and after processing embedded in paraffin to form blocks. 4 µm thick sections were cut and stained with H&E and Mallory's trichrome stains for morphometeric study.
Results: Highly significant increase in weight ($P<0.001$) was observed in animals of Group B and moderately significant ($P<0.01$) decrease was observed in Group C animals when compared to control and group B animals respectively. Cortical enlargement was found in zona glomerulosa and fasciculata and decreased thickness was observed in zona reticularis in Group B animals, when compared to control, the results were highly significant ($P<0.001$). In Group C decreased cortical thickness was noted in zona glomerulosa and fasciculata but in zona reticularis increase in thickness was noted when compared to Group B ,results were highly significant ($P<0.001$). Mallory's trichrome stained sections of Group B animals showed dilated blood vessels in the three cortical zones, more numerous in zona fasciculata when compared to control animals. In Group C no marked change was observed in all three cortical zones when compared to control.
Conclusion: L-Arginine restricts the excessive weight gain caused by high fat diet. It also ameliorates the hypertrophic and vasodilatory effects on adrenal cortex caused by high fat diet.
Key Words: High Fat Diet, Hypertrophic, L-Arginine.

INTRODUCTION

Obesity is characterized by excessive body fat accumulation[1]. Now a day it is considered a global epidemic and major public health problem. Its prevalence and tremendous cost of treatment necessitates the search for new alternative nutritional means[2]. Obesity decreases life expectancy and is associated with medical complications such as insulin resistance, type 2 Diabetes mellitus, Dyslipidemia, Hypertension and Atherosclerosis[3].

High fat diet, produces metabolic disorders in rats[4], and increases the susceptibility to the hyperglycemia. Liver showed increased expression of lipogenic genes and inflammatory markers. Elevated levels of corticosterone were also demonstrated in response to high fat diet [5]. Obesity and metabolic syndrome are associated with a state of chronic low grade inflammation in white adipose tissue, characterized by cytokine production and macrophage infiltration[6].

Key process involved in metabolic disturbances related to the obesity lies in the response of the hypothalamic-pituitary-adrenocortical (HPA) axis. The disturbances in the HPA axis functions play a permissive role in the metabolic disturbances associated with obesity[7]. Chronic exposure to glucocorticoid hormones also result in symptoms similar to the metabolic syndrome [8]. Differentiating adipocyte produce high levels of 11β-hydroxysteroid dehydrogenase type 1(11βHSD1) which converts inactive cortisone to active cortisol, thus increasing local glucocorticoid levels. Intracellular increase in glucocorticoids by the enzyme contributes to macrophage activation[9]. Chronic over nutrition might thus be a proinflammatory state with oxidative stress[10]. Hallmark of obesity and diabetes is a decrease in endothelial synthesis and bioavailability of nitric oxide. Physiological levels of nitric oxide play an important role in regulating the oxidation of energy substrate, insulin sensitivity and hemodynamics. Nitric oxide is synthesized from L-Arginine, underscoring a crucial role for this amino acid in maintaining health and treating a wide array of chronic diseases [11].

L-Arginine, a conditionally essential amino acid for adult mammal and is a precursor for the synthesis of biologically important molecules including nitric oxide, polyamines and agmatine etc [2]. L-Arginine increases expression of genes that promote whole body oxidation of energy substrates[12]. Nitric oxide (precursor of L-Arginine) regulates the metabolism of glucose, fatty acids and amino acids in mammals [13]. Physiological

levels of nitric oxide promote fat oxidation and decrease fat synthesis. L-Arginine supplementation reduces white adipose tissue mass by 20-40%, and decreases adipocyte size[14] and enhances lipolysis in adipocyte and lowers triglyceride and leptin levels[2]. Fat mass is also reduced in diabetic fatty rats[13].

L-Arginine treatment showed reduction in markedly increased blood glucose levels in diabetic rats. The polyamines, the product of L-Arginine, play a role in insulin biosynthesis and beta cell replication[15]. Nitric oxide is the key mediator of immune response. L-Arginine supplementation attenuates the oxidative stress induced by burn injury [16]. On adrenocortical cells, it significantly decreases both basal and adrenocorticotropic hormone (ACTH) induced corticosterone production in rats[17].

MATERIALS AND METHODS

Thirty male adult albino rats aged around 190 days weighing 200-230 gm were taken and kept on normal diet for one week observational period (12 hours dark and light cycle) before study.

The animals were divided into three groups, A, B, C (10 animals in each group) according to the diet they received. Group 'A' received normal diet. Group 'B' received high saturated fat diet (20 grams unsalted dairy butter/100 grams of normal diet, Lurpak, Denmark). Group 'C' received high saturated fat diet same as group B, along with L-Arginine (300mg/kg body weight/day, General Nutrition Corporation. Pittsburg, USA).

Animals were individually housed in plastic cages, and were kept on 12:12 hour light-dark cycle. Given food and water ad libitum. They were weighed at the initiation of study period, fortnightly and just before sacrifice. At the end of study period i.e. 8 weeks animals were dissected out after ether anaesthesia. Adrenal glands were excised, weighed and fixed in 10% buffered neutral formalin for 24 hours. After fixation they were processed in increasing strengths of alcohol, and were cleared with xylene and were infiltrated in paraffin. 4µm thick sections were cut with rotatory microtome. Sections were stained with H&E for morphometeric study and Mallory's trichrome stain for vascular pattern (dilatation of blood vessels).

Thickness of the three cortical zones was measured under 8 x ocular and 40 x objective with ocular micrometer in x and y axis from randomly selected 10 sections from each animal.

The statistical analysis was done by student's't' test and P-value less than 0.05 was considered as significant. Calculations were done by utilizing computer software SPSS version 13.

RESULTS

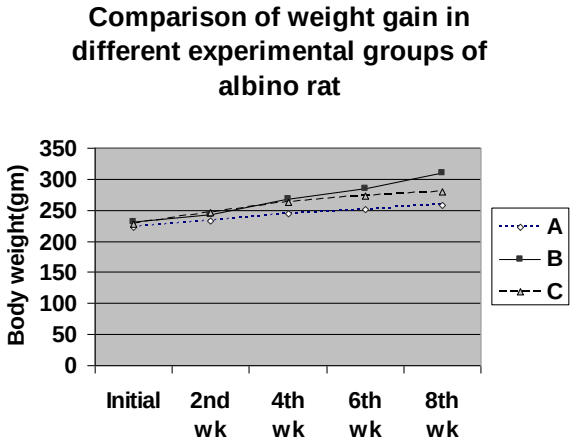
Highly significant (P<0.001) increase in weight was observed in animals of Group B when compared to control. Moderately significant (P<0.01) decrease in weight was observed in Group C animals when compared to group B animals.

Micrometry of H&E stained sections revealed the cortical thickness of three zones in different groups. There was highly significant (P<0.001) increase in thickness of zona glomerulosa observed in Group B when compared to control. Group C showed highly significant (P<0.001) decrease in thickness when compared to Group B as shown in Table 1.

Table-1: *Mean width of the three adrenocortical zones (µm) in different groups of albino rats

Groups	Zona Glomerulosa	Zona Fasciculata	Zona Reticularis
A	57.45±0.125	267.0±0.166	274.0±0.033
B	67.02±0.129	434.0±0.047	210.0±0.093
C	58.60±0.159	296.4±0.128	250.0±0.072

*Mean±SEM



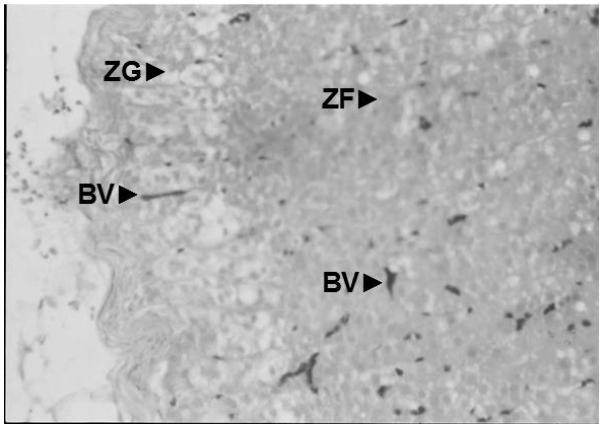


Figure No.:-1 Mallory trichrome stained 4µm thick section of adrenal cortex from group A rat, showing normal blood vessels. Photomicrograph x 400.

Zona fasciculata (ZF) of Group B when observed showed highly significant (P<0.001) increase in thickness compared to control. Group C showed highly significant (P<0.001) decrease in thickness when compared to Group B as shown in Table 1.

Zona reticularis of Group B animals showed highly significant (P<0.001) decrease in thickness when compared to control. Group C animals showed highly significant (P<0.001) increase in thickness when compared to Group B as shown in Table 1.

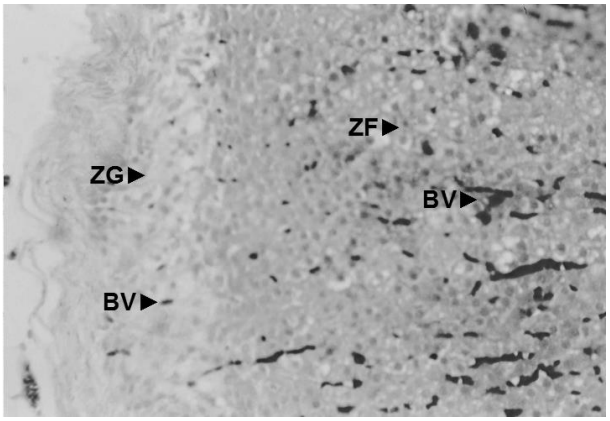


Figure No.:-2 Mallory trichrome stained 4µm thick section of adrenal cortex from group B rat, showing dilated blood vessels. Photomicrograph x 400.

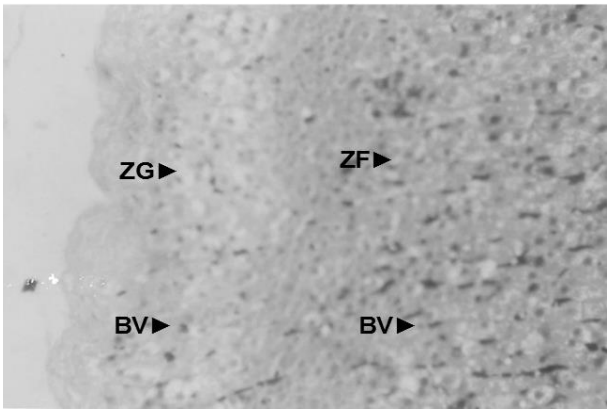


Figure No.:-3 Mallory trichrome stained 4µm thick section of adrenal cortex from group C rat, showing near to normal blood vessels. Photomicrograph x 400.

Mallory's trichrome stained sections of Group B animals (fig 2) showed dilated blood vessels in the three cortical zones, more numerous in zona fasciculata when compared to control animals (fig 1). In group C animals near to normal vascular pattern was observed in the three cortical zones (fig 3).

DISCUSSION

Obesity epidemic in developed countries caused financial burden on the economy of country[1]. Developing countries like ours couldn't afford lot of budget spent on treatment of such preventable disorder. Obesity and metabolic syndrome are multi-factorial disorders. Type of diet, genetic factors and hormones all play important role yet adrenal gland the end organ of hypothalamic pituitary adrenal axis (HPA) could not be ignored while considering these disorders[18]. Any agent which could affect the activity of adrenal gland may be helpful in the fight against obesity. L-Arginine, which has antioxidant properties, decreases fat mass[13,14]. It influences the hormonal synthesis in adrenal cortex[19].

Dietary interventional study in human indicates that high intake of fat contributes to the development of obesity [20], as the present study results showed that there was more weight gain in animals taking fatty diet. Woods et al (2003) found similar results when used butter oil in diet, with 10% increase in weight. Neilly et al (2009) in their study observed significant weight gain when given lard to animals, however they also observed increased adrenal weight and high corticosterone levels in these animals. Bjorntorp (2001) observed relationship of increased adrenal activity with increased visceral obesity and weight gain.

Decreased gain in weight in fat with L-Arginine receiving animals correlate well with other studies. Fu et al (2005) observed 16% lower weight in ten weeks study compared to control group, he gave L-Arginine in drinking water to obese diabetic Zucker rats. Jobgen et al (2006) observed reduced fat mass in diabetic fatty rats, while Jobgen and shi (2007) observed 20-40% reduced white adipose tissue mass in non diabetic rats with L-Arginine supplementation.

Adrenocortical hypertrophy more specifically zona glomerulosa and zona fasciculata was observed in fatty diet treated group, this finding indicates increased cortical activity. Gotohda et al (2005) observed cortical hypertrophy due to the stimulation of cortical cells as a result of toluene inhalation-induced stress. Hyperactivity of adrenocortical cells by biochemical analysis was observed by Widmaier et al (1995) who observed that high concentration of free fatty acid stimulates adrenocortical activity. Carsia et al (2008) compared the dietary effects of three different types of fats on adrenocortical activity by measuring hormonal contents and found that both corticosterone and aldosterone production increased in response to high saturated fat diet which is similar to the present study findings in which both zona glomerulosa and fasciculata showed hypertrophy in fat treated group.

Zona reticularis thickness was decreased in fat treated animals as a result of recruitment of zona reticularis cells into zona fasciculata (Kelly et al. 1998).

L-Arginine with fatty diet treated animals showed decrease thickness of zona glomerulosa and fasciculata probably because L-Arginine is a negative modulator of steroidogenesis in adrenocortical cells as mentioned by Repetto et al (2006). Cymeryng et al (2002) observed decreased activity of adrenocortical cells, both basal and ACTH stimulated, in response to L-Arginine treatment which is consistent with present study findings.

Mallory's trichrome stained sections revealed dilated blood vessels in fat treated animals. Obesity seems to

be a systemic low grade inflammatory state (Kyrou et al 2006), which together with ACTH release in response to high fat diet (Tannenbaum et al. 1997) leads to excessive vasodilatory effect observed in the vessels of adrenal cortex. Milovanovic et al (2003) observed the cortical vessels with Azan stain in response to ethanol administration, found dilated small blood vessels and prominent hyperemia.

L-Arginine, although a precursor of nitric oxide, which causes endothelial induced vasodilatation probably revert the inflammatory and ACTH induced excessive vasodilatation. Chattopadhyay et al (2009) observed the effect of L-Arginine on liver which decreased the congestion produced by ischemic reperfusion injury.

CONCLUSION

The study results confer to already existing evidence of adrenal cortex in its contribution to development of obesity and related problems. L-arginine although not the ultimate solution but, its observed role in reducing the stimulatory effects of fatty diet on adrenal cortex and preventable role in excessive weight gain supports its rightful role in the management of obesity and related issues. Further studies required for quantitative contribution of this organ keeping other causative factors in view.

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Original Article

Chronic Subdural Haematoma: Clinical Presentation and Surgical Outcome

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ABSTRACT

Objective: Chronic subdural hematoma having diversity of clinical features, poor index of suspicion and non availability of CT scan is still diagnosed very late in AJK.

The objective of study was to find out the clinical status at the time of admission and outcome of surgery in these patients managed in our hospital.

Study Design: Descriptive Study.

Place and Duration of Study: This study was conducted at the DHQ Hospital Mirpur AJK from March 2006 to April 2010.

Materials and Methods: A total number of 47 patients with chronic subdural hematoma of all age groups were operated at DHQ hospital Mirpur in this period. Clinical presentation of the patients at the time of admission was recorded. Patients were followed for a period of 2-3 months after surgery

Results: Forty seven patients were studied. Among them 40(85%) were male and 7(15%) were female. The age range was 2 months to 100 years with average age 52.5 years. Thirty one (66%) had positive history of head trauma whereas 16 patients (34%) did not remember any injury. Thirty one (66%) had headache, 35(74.5%) had hemiparesis, 19(40.4%) had behavioral changes and urinary incontinence. Six patients (12.8%) were having GCS 3 with reactive pupils. One (2.1%) patient came with decreased vision. CT scan showed unilateral hematoma in 37 (78.7%) and bilateral in 10 (21.3%) patients. Twenty five (53%) patients had hematoma on left side, 12(25.5%) had hematoma on right side and 10(21.3%) had bilateral hematoma. Thirty four (72.3%) had good recovery. Four (8.5%) could not survive.

Conclusion: Chronic subdural hematoma due to diversity of symptoms, poor index of suspicion, and non availability of CT scan is still diagnosed very late in AJK.

Elderly patients with diversity of confusing neurological symptoms need to be kept under high index of suspicion for diagnosis of chronic subdural hematoma. Drainage of Chronic subdural hematoma with two burr holes and placement of subdural drain offered excellent

Key words: Chronic subdural hematoma, Burr hole craniostomy.

INTRODUCTION

The incidence of chronic subdural hematoma (CSH) in the general population is approximately five per 100 000 per year, but is higher for those aged 70 years and older[1]. In elderly peak incidence at the age of 63 years[2] and in infants at 6 months[3] has been reported in some studies..

It is difficult to diagnose chronic subdural hematoma due to wide diversity of clinical features. In elderly it presents with features simulating neurological and psychiatric conditions like dementia, confusion, language difficulties ,hemiplegia, seizures, transient ischemic symptoms, and coma[4] Keen observations and high index of suspicion is necessary for diagnosis of subdural hematoma in these patients.

Often the only presenting sign of chronic subdural hematoma in infants is an accelerated increase in head size. Further investigation usually reveals some element of irritability, poor feeding, occasional vomiting, or tension of the anterior fontanelle[5].

The pathogenesis of chronic subdural hematoma is still a matter of debate and interest.

Among various theories the osmotic theory[6] and re bleed from the membrane around the clot[7] are important.

Computed tomography remains the primary imaging modality for diagnosing chronic subdural. MRI is highly reliable in diagnosing chronic and sub acute subdural hematoma[8]. Lesions that are isodense or hypodense on computed tomography generally appear hyperintense on both T1- and T2-weighted images**.**

Chronic subdural hematoma are treated by drainage by two burr holes[9] single burr hole[10] and twist drill craniostomy[11] Subdural drain can also be used postoperatively[12], usually 3 days of drainage is recommended for outer membrane of chronic subdural hematoma to restore a balance between coagulation and fibrinolysis[13].

Most of the patients return to their premorbid level of functions after treatment[14]. In children with evidence of increasing intracranial pressure, a subdural tap is performed, both for therapeutic decrease in pressure and for evaluation of the fluid for degree of blood content. If the pressure remains normal, more than one tap is usually not necessary. This tapping can be

repeated if there is recurrence of elevation in the pressure. If repeated taps do not resolve these collections, then a subdural peritoneal shunt is usually warranted[15].

Common complications associated with surgery include seizures, re-accumulation of hematoma, intracerebral bleed, pneumocephalus, and subdural empyema[16].

A mortality rate of 0-8% has been reported[10].

MATERIAL AND METHODS

It was a descriptive study carried out at DHQ hospital Mirpur AJK between March 2006 to April 2010.A total number of 47 patients with chronic subdural hematoma of all age groups were operated at DHQ hospital Mirpur in this period.

Patients of all age groups, who were diagnosed as subdural hematoma on CT scan, were included in the study. Patients were studied according to set protocol. All the patients had routine investigations done.

In the four pediatric patients repeated subdural taps were carried out which resolved the hematoma successfully. One patient who was symptomatic for more than 12 weeks, CT scan showed organized subdural hematoma, had craniotomy done. Rest of 42 patients were operated by two burr holes in unilateral and four burr holes in bilateral hematoma under local or general anesthesia.

All the patients received second generation cephalosporin preoperatively. Patients were positioned on the operation table keeping the head at the level of the heart. Local head shaving was done just before the incision. Incisions were marked depending upon the location and maximum thickness of hematoma. Area of incision was infiltrated with 2% xylocaine with0.001% adrenaline. Two burr holes one anterior and one posterior were made over the maximum thickness in unilateral hematoma. Dura was opened, hematoma drained (Fig 1A &B). Irrigation with isotonic saline was done till clear fluid came out. A subdural drain was placed in posterior burr hole and was taken out subcutaneously with different stab incision. For subdural drain soft feeding tube size 8-10 was used. The feeding tube was connected with drainage bag and connection was sealed with aseptic technique. Patients were shifted to ward keeping heads at the level of bed for 24-48 hours. Patients were hydrated well peri and postoperatively for rapid obliteration of subdural space[17]. Antibiotics were continued till drains were removed. Drains were removed when fluid drain was less than 30 ml in 24 hours. Drains were removed between 24-72 hours.

Patients were discharged 5-7 days after surgery. They were followed monthly in out patients for the period of 2-3 months.

RESULTS

Forty seven patients were operated. Among them 40 (85%) were male and 7 (15%) were female. The age range was 2 months to 100 years with average age of 52.5 years.

Fourteen patients (29.8 %) were infants, 13 patients (27.7 %) were between 71-80 years, 8 patients (17%) were between 51-60 years and only one patient (2.1%) was 14 years old. (Table 1)

Table No.1: Age Distribution

Age	No of Patients
Infants (Less than 2 years)	14 (29.8%)
14 years	1 (2.1%)
51-60 years	8 (17 %)
61-70	2 (4.2 %)
71-80	13 (27.7 %)
81-90	5 (10.6 %)
> 90 years	4 (8.5 %)

Table No. 2: Clinical Presentation of patients

Clinical presentation	No of patients
Hemiparesis	35(74.5%)
Behavioral changes	19(40.4%)
Urinary incontinence	19(40.4%)
Headache	16(34 %)
Irritibility, vomiting, buldging fontanel	6(12.7%)
Coma	6(12.7%)
Reduced vision	1(2.1%)

Table No. 3: Outcome

Neurological Grade	No of patients
Death	4 (8.5%)
Moderate disability	9(19.1%)
Good recovery	34(74.3%)

Thirty one patients (66%) had history of head trauma .Eighteen patients (38. %) had duration of symptoms for 2-4 weeks,17 patients had 4-8 weeks ,9 patients had less than 2 weeks whereas one patient had duration of symptoms more than 12 weeks. (Figure 2) Headache were present in 16 (34%), 19 patients (40.4 %) had behavioral changes, 35 patients (74.5 %) had hemi paresis, 19 patients (40.4 %) had urinary incontinence. Six patients (12.8%) were in coma and one 16 years old patient was referred to us with decreased vision and papilloedema. Six pediatric patients (12.7%) had irritability, vomiting and buldging fontanelle. (Table 2)

Thirty six patients (63.8 %) had GCS 13-15 on admission, 11 patients (23.4 %) had GCS 8-12, whereas 6 patients (12.8 %) had GCS 3-7.

Thirty seven patients (78.7 %) had unilateral hematoma 10 patients (21.3 %) had bilateral hematoma. Hematoma was on left side in 25 patients (53.2 %), 12 patients (25.5 %) had on right side and it was bilateral in 10 (21.3 %) Four pediatric patients (8.5 %) were

managed with repeated subdural taps in OT. Four patients (8.5 %) were operated under local anesthesia whereas rest of 39 patients (82.9 %) was operated under general anesthesia. Four patients (8.5%) had postoperative intracranial bleed, 2 of them were hypertensive and 2 had associated bleeding disorders. These patients detoriated rapidly and did not survive. Five patients (10.6%) had postoperative seizures which were managed conservatively.

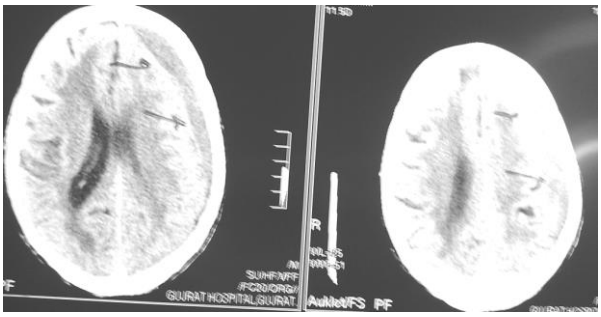

Figure 1 A: CT scan brain of 85 years old comatose patient with subdural hematoma

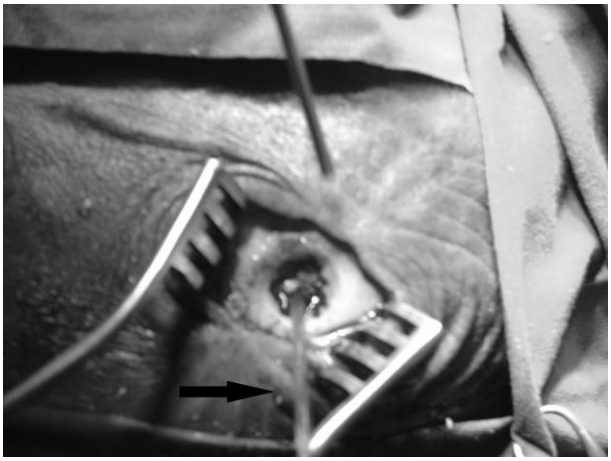

Figure 1 B: High pressure stream of subdural hematoma on opening dura in the same patient

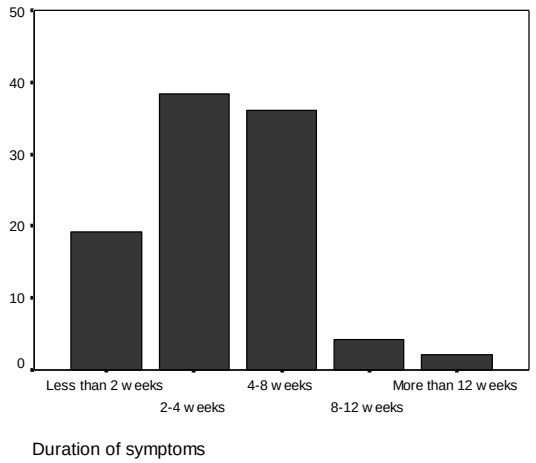

Figure 2: Graph showing duration of symptoms in percentage of cases

At the time of discharge 34 patients (74.3 %) showed good recovery (Grade V on Glasgow out come score), 9 patients (19.1 %) had moderate disability (Grade IV on Glasgow out come score), and 4 patients expired (Grade I) (Table 3).

DISCUSSION

Chronic subdural hematoma is a common clinical entity encountered in daily neurosurgical practice in pediatric and elderly patients[1,2]. Due to its diversity of clinical presentations, it is difficult to diagnose clinically.(4,5)

The incidence of chronic subdural hematoma is not well documented; it has been reported as 5 per 100000 populations with highest of 7.35 per 100000 in the age group between 70-79 years[3]. In the infants peak incidence reported at 6 months of age[2].

In this study youngest patient was 2 months old while the oldest patient was 100 years old. Among these patients 14 patients (29.8 %) were infants. Among adult 32 (68 %) patients, highest incidence was between 71-80 years (27.7%), followed by 51-60 years (17 %,), 81-90 years (10.6%) whereas 8.5% patients were between 91-100 years. This age incidence is in line with other studies[1,4].

Forty patients (85%) were male and 7 (15%) were female with male to female ratio of 6:1.

Male preponderance has been reported in various studies[18]. In females lesser exposure to trauma and estrogen defensive effect on blood vessels is said to be the reason for less incidence[18].

Thirty one (66 %) patients had positive history of head trauma. Four patients were hypertensive, and on anti thrombotic treatment. Falls and anti thrombotic therapy are reported as most frequent risk factors for chronic subdural hematoma[19].

The average time between injury and onset of symptoms is 6 weeks (20).These patients are usually diagnosed very late due to diversity of clinical picture and especially in the areas where CT scan is still not available.

Only 9 (19.1 %) patients in this study reported with in 2 weeks of onset of symptoms .Eighteen patients (38.3%) had symptoms for 2-4 weeks a 17 patients (36.2 %) had 4-8 weeks 2 patients (4.3 %) had 8-12 weeks. One patient 14 years old was symptomatic for more than 12 weeks was referred to us by ophthalmologist for reduced vision and papilloedema. Six patients (12.8%) who were symptomatic for more than 4 weeks were brought in coma.

This delayed presentation of our patients even compared with another local study (21) carried out at Islamabad is for the reason that Chronic subdural hematoma is less suspected by general practitioners and CT scan is still not available in peripheral areas of **AJK.:** Majority of patients (74%) had hemiparesis,

followed by behavioral changes and urinary incontinence (40.4%).Headache was only in 34% patients. Low incidence of headache compared to other studies[4,21,22] may be due to inclusion of pediatric and comatose patients where proper history was not available.

Best method of treating chronic subdural hematoma is still matter of debate. Chronic subdural hematoma are being drained by two burr holes, single burr hole, and twist drill craniostomy[9,10,11]. Placement of subdural drain is also controversial. In some studies they conclude that leaving drain is better to reduce the recurrence[4,22, 23].

Some recommend subdural drains for 3 days (13) whereas other authors are in opinion that there is no significance between recurrence in keeping or not keeping the drains[24].

In one local study, they concluded that placement of subdural drain caused increased rate of infection, brain injury and post op seizures[25].

In this study 4 pediatric patients were successfully managed by repeated subdural taps under aseptic techniques in operation theatre. One teen age patient who had more than 12 weeks symptoms of headache and decreased vision was managed by craniotomy because CT scan showed thick membrane. Rest of 42 patients had two burr holes for unilateral hematoma and four burr holes for bilateral hematoma. Subdural drain was placed for unilateral and two drains for bilateral cases. Drains were removed 24-72 hours when drainage was less than 20 ml. We did not have any incidence of recollection or infection.

Five patients (10.5%) had post operative seizures, which were managed conservatively. Four patients developed postoperative intracerebral bleed, two of them were hypertensive and two had added bleeding disorders. These patients detoriated rapidly and did not survive. High mortality as compared to other studies (4,24,25) was related to patients systemic problems.

At the time of discharge 34 patients (74.3%) were back to premorbid neurological status (Glasgow outcome score Grade V) 9 patients (19 %) hade moderate disability (Glasgow outcome score grade IV) Mortality was 8% (Table 3).

CONCLUSION

Chronic subdural hematoma due to diversity of symptoms, poor index of suspicion, and non availability of CT scan is still diagnosed very late.

Most of these patients presented with hemiparesis, headache, behavioral changes and urinary incontinence.

Elderly patients with diversity of confusing neurological symptoms need to be kept under high index of suspicion for diagnosis chronic subdural hematoma.

Drainage of Chronic subdural hematoma with two burr holes and placement of subdural drain offered excellent results.

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Original Article

The effect of multiple risk factors on the Severity of Coronary Artery Blockage among the Patients who had undergone Angiography in the Cardiology Unit of JHL

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ABSTRACT

Introduction: Coronary artery disease (CAD) is the leading cause of mortality in the elderly. Traditional cardiovascular risk factors (CVRFs) such as advancing age, diabetes mellitus, hypertension, dyslipidemia, smoking, obesity, and family history of CAD are well recognized for their association with clinical events and acute coronary syndromes; however, the correlation between CVRFs and atherosclerotic burden, assessed angiographically, is not as well established, with the studies reporting variable and inconsistent results.

Objectives: To study the effect of multiple risk factors on the severity of coronary artery blockage among the patients who had undergone angiography.

Study Design: A Descriptive Cross Sectional Study.

Place and Duration of Study: This study was carried out at Cardiac Unit Jinnah Hospital Lahore from May 2010 to July 2010.

Material & Methods: The study included 120 patients undergoing angiography and were assessed for severity of risk factors. Cross tabulation was performed with dependent variable, severity of coronary artery disease and independent variables like familial tendency, smoking, Diabetes, hypertension, obesity and high cholesterol level. Chi square test was applied to see statistical significance.

Results: Severity of coronary artery disease was assessed by number of coronary vessels involved. Vessels with more than 50% blockage on angiography were labeled as blockade .Among them 42 % of the subjects had one vessel involved and 78% of the subjects had more than one vessel involved. Mean age of subject were 53.0 yrs with SD + 11.7. 76.7 % were male and 23.3 % were female. 49.2 % had familial history of Coronary artery disease 66.7 % were smokers. 38.3 % of subjects had diabetes mellitus. 68.3 % of the subjects had hypertension. 37.5 % of the subjects were overweight . 17.5 % of the subjects had cholesterol level > 250 mg/dl 75.8% of the subjects had a proximal blockade, 20.0 % had a distal blockage and 4.2 % had both proximal and distal blockage. Smoking , duration of smoking, number of cigarettes smoked per day and obesity are positively associated with severity of coronary artery disease and are statistically significant ($P < .05$). While high cholesterol level, diabetes and Hypertension had a non-significant relationship in our study..

Conclusion: There is a significant association between the severity of risk factors and the severity of coronary artery disease. The association of Smoking , duration of smoking, number of cigarettes smoked per day and obesity with severity of coronary artery disease is statistically significant ($P < .05$).

Key words: Coronary blockage, Risk factors, Coronary artery disease, Coronary Angiography.

INTRODUCTION

The commonest cause of myocardial ischemia is reduction in coronary blood flow due to atherosclerotic coronary arterial obstruction. Thus, Ischemic Heart Disease (IHD) is often termed Coronary Artery Disease (CAD) or Coronary Heart Disease (CHD). IHD is the generic designation for a group of closely related syndromes resulting from myocardial ischemia. These syndromes are the late manifestations of coronary atherosclerosis that probably began during childhood or adolescence.[1,2]

The clinical manifestations of IHD can be divided into four syndromes. Myocardial Infarction (MI), Angina, Chronic IHD causing heart failure and sudden cardiac death. The prevalence and severity of the disease among individuals and groups are related to a number of factors, some are constitutional but others acquired and potentially controllable. The risk factors that predispose to atherosclerosis and resultant IHD have been identified by means of a number of prospective studies in well defined population groups; multiple risk factors may have a multiplicative effect.[3,6] Age, gender and family history are non modifiable risk factors whereas hyperlipidemia, hypertension ,cigarette smoking, diabetes and obesity are modifiable risk factors.

People of Indo-Asian origin have one of the highest susceptibilities to coronary artery disease (CAD) in the world, and it is therefore unsurprising that CAD is now the leading cause of death in the Indo-Pakistan subcontinent.[4]

Coronary artery disease (CAD) is the leading cause of mortality in the elderly, and more than 80% of the mortality due to CAD occurs in persons older than 65 years. Traditional cardiovascular risk factors (CVRFs) such as advancing age, diabetes mellitus, hypertension, dyslipidemia, smoking, obesity, and family history of CAD are well recognized for their association with clinical events and acute coronary syndromes; however, the correlation between CVRFs and atherosclerotic burden, assessed angiographically, is not as well established, with the studies reporting variable and inconsistent results.[5-7] We designed this study to compare the severity of risk factors with the severity of coronary blockage, to assess the hypothesis that "The risk factors are more severe in patients who have severe coronary blockage as compared to the ones who have mild to moderate blockage.", and to identify those patients who have increased severity of risk factors so that they can be given intensive care.

MATERIAL AND METHODS

A descriptive cross sectional study was carried out at Cardiac Unit Jinnah Hospital Lahore from May to July 2010.The study included 120 patients undergoing angiography through purposive sampling technique. Minimum sample size was estimated using WHO statistical software Epi-info.The expected Odd's ratio with smoking as risk factor was taken as 3.5 at 80% power and 95% significance level. Calculated sample size was 115 rounded off to 120.

After informed consent detailed demographic characteristics clinical history was taken. Risk factor evaluation and severity was done according to operational definitions. Coronary artery disease severity was categorized after their angiography findings (Vessels with more than 50% blockage on angiography were labeled as blockade) and severity was categorized according to number of vessels involved.

Data was entered and analyzed in SPSS. Frequency and percentage were tabulated for severity of coronary blockage and risk factors. Cross tabulation was done between severity of coronary blockage and risk factors severity and chi square was applied to assess the statistical significance.

RESULTS

In this study 120 subjects undergoing coronary angiography were selected. Mean age of subject were 53.0 yrs with SD $\pm$ 11.7. 29.2 % of the subjects were less than 45 years of age, and 70.8 % were more than 45 years of age. 76.7 % were male and 23.3 % were female. 92.5 % of the subjects were married and 7.5 % were single.

49.2 % of the patients had familial history of Coronary artery disease among them 56.0 % had one or both parent with coronary artery disease,30.5% had a sibling with coronary artery disease and 13.5 % had both. 66.7 % were smokers. Among them 30.0% smoke 5-10 cigarettes per day, 62.5% smoke 10-30 cigarettes per day and 7. 5% were smoking more than 30 cigarettes per day. 12.5 % were smoking for 5 years, 23.8% were smoking for 5-10 years and 63.7 % smoking for more than 10 years.

Table No.1: Frequency of Risk Factors and Severity of Coronary Artery Disease.

Variables		Frequency	%age
Severity	Severe	78	65%
	Less severe	42	35%
Smoking	Smoker	80	66.7%
	Non-smoker	40	33.3%
Obesity	Obese	56	46.7%
	Non-obese	64	53.3%
Diabetes	Diabetic	46	38.3%
	Non-diabetic	74	61.7%
Hyperten-sion	Hypertensive	82	68.3%
	Non-hypertensive	38	31.7%
Cholesterol	200-250mg/dl	99	82.5%
	>250mg/dl	21	17.5%
Family history	Yes	59	49.2%
	No	61	50.8%
Age	<45	35	29.2%
	>45	85	70.8%
Gender	Male	92	76.7%
	Female	28	23.3%
Number of cigarettes	<10-10/day	24	30%
	>10/day	56	70%
Duration of smoking	<10-10 yr	29	36.2%
	>10 yr	51	63.8%

Among patients who showed a severe pattern of disease on angiography 37.25 were diabetics and 62.8% were non diabetics. 74.4% were smokers and 25.65 were non smokers . 67.9% were hypertensive and 32.1% were non hypertensive 44.9% were obese and 55.1% were non obese. 79.5% had high cholesterol level and 20.5% had normal levels .Severity of coronary blockage is found to be associated with smoking history, number of cigarettes smoked per day, duration of smoking and obesity. 72.5% of patients who smoked for more than 10 yrs showed severe disease as compared to 27.5% of patients who smoked for less than 10 yrs and developed severe disease.(table 2). Among those who developed severe disease 18.4% were moderate smokers (<10 cigarettes/day) whereas 81.1% were heavy smokers

(>10 cigarettes/day) (table 2). 55.1% of patients with severe disease were obese and 44.9% were non-obese .
Cross tabulation was performed with dependent variable, severity of coronary artery disease and risk factors like familial tendency, smoking, Diabetes, hypertension, obesity and high cholesterol level. Chi square test was applied to assess association. The association of severity of coronary artery disease with smoking , duration of smoking, number of cigarettes smoked per day and obesity is found to be statistically significant (P<.05)(table 2). While high cholesterol level, diabetes and Hypertension had a non-significant relationship in our study.

Table No.2: Statistical Analysis of Risk Factors and Severity of Coronary Artery Disease.

Risk factors	Count & %	Severity		Total	P value for chi-square/ Fisher exact and Odd's Ratio
		Less Severe	Severe		
Smoker	Count	22	58	80	P =0.015 OR=2.64
	%	52.4%	74.4%	66.7%	
Obese	Count	13	43	56	P=0.01 OR=2.74
	%	31.0%	55.1%	46.7%	
Diabetic	Count	17	29	46	P=0.72 OR= 0.87
	%	40.5%	37.2%	38.3%	
Hypertensive	Count	29	53	82	P= 0.902 OR=0.95
	%	69.0%	67.9%	68.3%	
Hypercholestrolemia	Count	37	62	99	P=0.237 OR=1.91
	%	88.1%	79.5%	82.5%	
Age>45	Count	26	59	85	P=0.114
	%	61.9%	75.6%	70.8%	
Family history positive	Count	21	38	59	P=0.893
	%	50.0%	48.7%	49.2%	
Number of cigarettes >10/day	Count	9	47	56	P=0.001
	%	41.0%	81.1%	70.0%	
Duration of smoking >10 Yrs	Count	9	47	56	P=0.001

DISCUSSION

Our research is related to the comparison of severity of risk factors to severity of coronary blockage in patients undergoing angiography, the risk factors were familial tendency, smoking history, DM, HTN, obesity and cholesterol level. Researchers have shown that lifestyle change, including Physical activity, a healthy diet, and smoking cessation, alters the course of CHD severity[8], In a meta analysis, fifteen studies reported diet as an outcome, with a total of 51 outcomes. Of these, 39 showed significant benefits for intervention patients compared to controls in relation to dietary consumption. These included significant improvement in specific food intake, such as fat, fibre , sugar, and cholesterol, diet score, diet knowledge, and habits, and for concern about dietary habits.[9] These studies are consistent with our finding that obesity is positively associated with CAD. Obesity can be well controlled through life style modifications and dietary changes. In our study smoking, duration of smoking and number of cigarettes smoked per day show strong association with severity of coronary artery disease. While all studies reported proportions of the study populations that smoked, only 13 studies reported smoking as an outcome and five of these reported significant reductions in smoking behaviors in the intervention groups[10]. Few studies reported a non-significant difference between intervention and control groups at one year, but significant at two and three years.[10-.13] Thirteen studies reported BP as an outcome, and five reported significant benefits for intervention compared to control patients . Giallauria et al reported significant improvements in SBP and DBP at 12 months and 24 months.[14] Redfern et al reported significant difference in SBP among intervention compared to control patients at three months and 12 months.[15] Campbell et al collected BP data from medical records and classified it as being managed according to British Hypertension Society recommendations if the last recorded measurement was less than 160/90 mmHg or receiving attention. The significant difference between intervention and control groups at one year was no longer observed at four-year follow-up.[16] Total

Cholesterol and/or Lipid Levels outcomes were reported by 19 studies and 12 demonstrated significant benefits for intervention patients. Seven of these 12 studies reported significant improvements in total cholesterol for intervention patients compared to control.[12-]

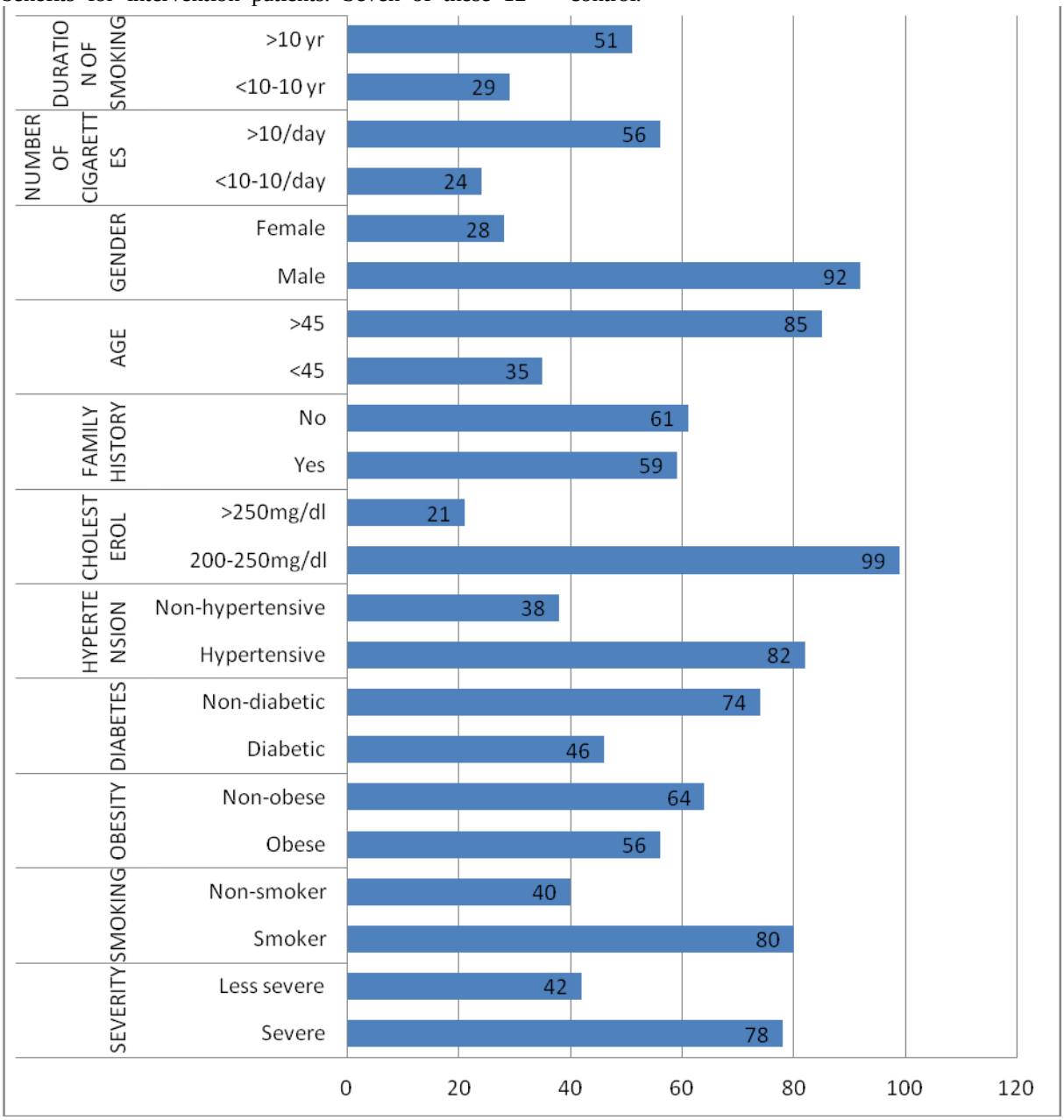

Figure: Percentage of Severity and Risk Factor

In our study association of hypertension, diabetes and high cholesterol levels has not come out to be significant though many studies have shown them to be positively associated. This deviation can be attributed to limited sample size. Thus, this area requires further exploration.

CONCLUSION

The conclusion of this study is that there is a significant association between the severity of risk factors and the severity of coronary artery disease. Patients having multiple risk factors have severe coronary artery disease. Smoking, duration of smoking , number of cigarettes smoked per day and obesity have significant effect in severity of coronary artery disease as individual factors.

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Original Article

Microflora of Bile Aspirates and its Antibiogram

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ABSTRACT

Objective: To determine the frequency of bacterial infection in patients presenting with Cholelithiasis.
Study Design: Descriptive case-series study.
Place and Duration of Study: This study was carried out in the Surgical Unit Nishtar Hospital, Multan from October 2007 to September 2008.
Materials and Methods: All adults patients aged 20 years and above who were admitted with a provisional diagnosis of cholelithiasis, over a period of one year were entered into the study. The study included 100 patients between the ages of 20 and 60 years.
Results: The 100 patients who presented with cholelithiasis underwent operation and bile was taken for culture and sensitivity. There were 88 women (88%) and 12 (12%) were men. Age was ranging from 20 to 60 years (mean 44.4 years). 56 (56%) were operated laparoscopically while in 44 (44%) open cholecystectomy was done. Out of 100 bile culture 16 (16%) were positive while in 84 (84%) cases no growth cultured.
Conclusion:.In patients of cholelithiasis bile may be infected and infection may be causative factor in formation of gall stones. Most of the microorganism were sensitive to cefuroxime axetil and ceftrioaxone.
Key words: Bile culture, Cholelithiasis, E.Coli.

INTRODUCTION

Gallstones are abnormal masses of a solid mixture of cholesterol crystals, mucin, calcium bilirubinate, and proteins that have affected people for centuries:[1] Multiple gallstones were found in a mummified Egyptian priestess[2], but the disease was first described in 1507 by a Florentine pathologist, Antonio Benivenius[3].

The Swiss medic Paracelsus viewed gallstones as a consequence of "tartaric" disease. With a prevalence of 10–15% in adults in Europe and the USA, gallstone disease is one of the most common and most expensive to treat of digestive disorders that need admission to hospital[4]. Every year in the USA, more than one million people are newly diagnosed with gallstones, and about 7,00,000 individuals have cholecystectomies[5]. In 1882, in the first open cholecystectomy Langenbuch successfully removed the gallbladder of a 43-year-old man who had had gallstones for 16 years. This technique remained the gold standard therapy for symptomatic gallstones for over a century, although medical treatment with bile acids was first described in the late 19th century[6].

After a report of complete dissolution of gallstones by bile acids in 1937[7], oral bile acid litholysis with chenodeoxycholic acid as a method for removing cholesterol gallstones emerged in the 1970s[8], and litholysis with ursodeoxycholic acid in the 1980s. Extracorporeal shockwave lithotripsy plus oral bile acids for symptomatic gallstones was introduced first in 1986 in Munich[9].

Later, several studies proved that gallstones recur in 30–50% of cases, 5 years after bile salts therapy or lithotripsy[10]. In 1987, Mouret undertook the first laparoscopic cholecystectomy, which is today the treatment of choice for symptomatic gallstones. In the human gallbladder, three types of gallstones exist, depending on the major constituents: pure cholesterol, pure pigment, and mixed (small amounts of calcium and bilirubin salts).

Pigment stones appear in two major forms: black and brown. Whereas black pigment stones result from haemolysis and consist primarily of calcium bilirubinate, brown pigment stones are associated with infections of the biliary tract (bacterial and helminthic) and are more frequent in Asia or occur after cholecystectomy as de novo common bile duct stones.[18] Cholesterol gallstone disease results from a complex interaction of genetic and environmental risk factors. Infection plays a major role in formation of gall stone and bile may not be sterile in patient with cholelithiasis The purpose of the study was to determine the microflora of bile aspirates and its antibiogram.

MATERIALS AND METHODS

Patients of Cholelithiasis admitted through out patient department [OPD]. Patients who were about to undergo cholecystectomy were selected from the ward. Ultrasound of abdomen was done on every patient to confirm the diagnosis of cholelithiasis. Informed consent was taken from the patient and patient was briefed about study and confidentiality was maintained. It was also ensured that no risk is involved to the patient in this study. History was taken from the patient about pain right

hypochondrium, dyspepsia, nausea, vomiting, jaundice, fever, weight loss.

Examination of patient was done for pulse, temperature, jaundice, tenderness or mass in right hypochondrium.

Certain basic investigations like complete blood count, random blood sugar, liver function tests, renal parameters and specific investigations like ultrasound of abdomen was done.

A dose of prophylactic antibiotic was given to the patient at the time of induction of anesthesia. Patients ware operated under general anesthesia in supine position. After opening/entering the abdomen and confirming the diagnosis bile aspirated from the fundus of gall bladder in 5cc syringe. All specimens were sent to the department of pathology for culture and results were recorded on a proforma.

RESULTS

The 100 patients who presented with Cholelithiasis underwent operation and bile was taken for culture and sensitivity. There were 88 women (88%) and 12 (12%) were men. Age was ranging from 20 to 60 years, mean 44.4 years (Table-1).

In all patients, 56 (56%) were operated laparoscopically while in 44 (44%) open cholecystectomy was done (Table-2).

Out of 100 bile culture 16 (16%) were positive while in 84 (84%) bile culture was negative (Table-3).

Most of bacteria were sensitive to cefuroxime axetil [second generation cephalosporin] and ceftriaxone sodium [third generation cephalosporin].

Table No. 1: Age distribution (n=100)

Age (Years)	No. of patients	%age
20-30	18	18.0
31-40	42	42.0
41-50	26	26.0
51-60	14	14.0

Table No.2: Procedure of surgery (n=100)

Procedure	No. of patients	%age
Laparoscopic cholecystectomy	56	56.0
Open cholecystectomy	44	44.0

Table No.3:Status of patients (n=100)

Status	No. of patients	%age
Positive	16	16.0
Negative	84	84.0

DISCUSSION

Gallbladder disease is the commonest indication for abdominal surgery and is the second most common intra abdominal operation performed in the western countries[11]. Gall stones are responsible for more than 95% of biliary tract disease[12].

Different factors have been implicated in the causation of gall stones amongst which infection of the bile is also as important factor. In about 30% of the patients with cholelithiasis, bacteria can be cultured either from the bile or from the wall of the gallbladder. The biliary infection can be caused by any type ranging from aerobic gram positive to gram negative to anaerobic organisms. Aerobic organisms cause 94% of biliary tract infections while anaerobic organisms cause the rest.

Bacteria are commonly found in inflamed gallbladder and in patients with cholelithiasis, whereas evidence suggests that normal bile is sterile[13]. Inflamed gallbladder has markedly altered permeability, which permits absorption of bile acids and movement of inorganic salts into the gallbladder lumen.

The role of excessive cellular debris and increased protein secretion, which occurs in response to inflammation, may be present. Finally, bacterial enzymes effects constituency of bile which may alter its solubility leading to precipitation of bile salts. Most gall stones are composite in nature. Bacteria can be found in most pure stone (i.e. those whose structure consists more than 90% cholesterol). The natural history of gall stones is unknown. It is likely that brown pigment stones can evolve in their chemical composition after termination of the infection process that initiate their formation, and may further develop into either mixed or nearly pure cholesterol stones. It is difficult to ascertain that whether bacterial infection of bile arose from stone formation or vice versa.

Although the exact contribution of bacteria in lithogenesis is not known, it is important for the clinician to realize that most gall stones are likely to be colonized by bacterial biofilm, even though the bile may be culture negative.

Cholecystitis and cholelithiasis are prevalent in certain regions of the world and quite rare at other places. Hence, these are sometimes called South Western American disease[19] and has been reported in 54% of the adults above 21 years of age[14].

A bacterial cause of cholecystitis has been proposed and positive bile cultures have been noted in 46% of patients with acute cholecystitis. In one study from Germany, using molecular genetic methods, bacteria could be found in most pure cholesterol stones (i.e. those whose structure consists of more than 90% cholesterol)[15]. It is suggested that bile infection by E. coli, in addition to bile stasis, plays a crucial role in the pathogenesis of brown pigment stones[16]. Bacterial DNA sequences are usually present in mixed cholesterol, brown pigment, and common bile duct, but rarely in pure cholesterol gallstones[17]. Interest has continued to abound in the role of infection in cholelithiasis. Two fallacies, however, exist in this

regard. Firstly, the culture of the organism from the bile at the time of the operation does not necessarily indicate a cause effect relationship between the infective microorganism and lithogenesis, as infection may be secondary to calculus formation. Secondly, the failure to isolate organism from bile also does not indicate that the etiology is unrelated to the infection as it is well-known that organisms which have initiated the stone precipitation may not persist in the viable form in the bile till surgery.

This study shows that this disease is much more common in females as compared to the males. The mean age incidence in this series is 48 years in females and 44 years in males.

Iqbal et al. in 2001 reported maximum number of patients with cholelithiasis between the age of 20 – 30 years with the highest incidence of choledocholithiasis accompanying cholelithiasis in 61–75 years of age[18].

In this series, the positive bile culture was 36%, which is considerably higher than that reported by Yaqin and Sultan[19].

However, more recently Sabir[30] has reported an incidence of 16%. Harbi[20] in 2001 reported 25% and Csendes reported 46%[21]. Van Leeuwen from Kuwait showed positive bile cultures in 16.4% and 19 different bacterial species were identified[22]. Guo from China showed the incidence of bacteria to be very high, ranging from 20 to 96%, with an average of 66.7% depending on the kind of gallstone present[23]. Therefore, infection is likely to range from 16 to 96 % which corroborates with the present finding.

CONCLUSIONS

In patients of Cholelithiasis bile may be infected and infection may be causative factor in formation of gall stones. E. Coli is most common organism found in bile culture as in many other national and international studies.

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Original Article

How much Blood Transfusion Protocols Are Followed among Health Care Providers in the Tertiary Care Hospitals of Rawalpindi and Islamabad

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ABSTRACT

Objective: The high-ceilinged importance given to safe blood transfusion, a study was conducted in the teaching hospitals of Islamabad and Rawalpindi to ascertain how much blood transfusion protocols are followed.

Study Design: Cross sectional study.

Place and Duration of Study: This study was carried out in the Teaching Hospitals of Islamabad and Rawalpindi, between Oct, 2007 to Dec, 2007

Materials and Methods:, A total of seventy six health care professionals from surgical and allied specialties were put forward a questionnaire Performa relating to as to whether departmental guidelines for blood transfusion are followed or not.

Results: Out of total studied sample i.e. seventy six in total, forty health care personals i.e. 52.63% affirmed that they do follow departmental guidelines for blood transfusion, whereas thirty six personals i.e. 47.37% were lacking the follow-up of standard protocols in their settings.

Conclusion: In the study 47.37% i.e. thirty six in number of considered health care professionals were of the opinion that they do not pursue in spirit departmental guidelines regarding blood and blood product transfusion.

Key Words: blood transfusion; protocols of blood transfusion.

INTRODUCTION

The major indication for blood transfusion is prevention and treatment of tissue hypoxia by increasing oxygen carrying capacity of blood. Transfusion requirements of each patient should be based on clinical status or considering serial hemoglobin level or hematocrit concentrations.

According to a survey conducted by the Committee on Blood and Blood Products of the American Society of Anesthesiologists, anesthesiologists administer more than half of all blood given to the patients.[1]Few risks of blood transfusion include immunological i.e. hemolytic reaction—being most fatal among all, which result from misidentification of sample, transfusing unit or patient itself.[2] Febrile and urticarial reactions belong to non-hemolytic group of complications, which also include the notorious ones like, transfusion related acute lung injury and is the most commonest cause of morbidity and death after transfusion. It presents as an acute respiratory distress syndrome either during or within six hrs of transfusion[3], transfusion related autoimmune neutropaenia in neonates [4] and suppression of erythropoietin in premature infants.[5] The study done by Ali SI and colleagues stated transfusion related acute lung injury as a devastating complication of blood or its components transfusions irrespective of the blood grouping and cross match and it is not an uncommon complication[6].

Blood transfusions save the lives of incalculable numbers of people suffering from shock, hemorrhage, or blood diseases. It is employed routinely in cases of surgery, trauma, gastrointestinal bleeding, and in childbirths that involve great loss of blood world-wide every day. It is an integral aspect of modern medical care and best transfusion practice means transfusing a patient when there is an identified clinical need and not transfusing when there is no clear clinical indication. It is also a mean of maintenance of adequate intravascular volume while limiting the complications of severe blood loss. Therefore following the Protocols for blood transfusions may be an effective way to improve outcome, promote decision consistency and reduce the number of inappropriate blood transfusions, and thus help save lives or improving the patient's condition.

Consideration of adverse effects of blood transfusion, any transfusion reaction means that the transfusion is not performing the intended job and, importantly, has burdened a patient already burdened by the physiologic state requiring transfusion. Sensitization to blood cells can result in refractory results in subsequent transfusions. Transfusion of multiple units of whole blood sequentially in order to achieve a certain hematocrit may also produce pulmonary edema due to volume overload. Furthermore, transfusions dampen the physiologic response to deficiency of a blood constituent. For example, if a patient has a low red cell mass, tissue hypoxia results in increased erythropoietin

production and the marrow responds with reticulocytosis. Red cell transfusion, in this patient, will result in diminished and delayed reticulocyte response. Several questions should be considered prior to transfusion.1) Is blood transfusion really necessary? 2) What is the patient's particular need? 3) Does the prospective benefit justify the risks of transfusion? 4) What blood component will effectively meet this special need at the lowest cost? And after transfusion: did the transfusion result in the anticipated benefit for the patient? Answers to these questions should be documented in the patient's record. The basic principle in transfusion therapy is the same as in all medical approaches, "primum non nocere" - first do no harm. The blood transfusion protocols guide in employment of evidenced-based transfusion guidelines answering the stated questions.

In study done by Kanwal S and colleagues[7], at MCH Center PIMS, Islamabad, from Oct-Dec 2005, out of total admissions i.e. one thousand nine hundred and twenty, 206 patients (10.7%) were advised to arrange blood and 166 (8.6%) patients received blood transfusions. The obstetric patients were 132 (64%), 114 patients arranged blood and 106 received transfusions. Transfusion rate was 7%. Total units arranged were 272, and units transfused were 244, the number of transfusion per patient were 2.3 units. The two major indications for transfusion were chronic anemia and acute hemorrhage in 62(58.4%) and 44(41.5%) patients respectively. However 28(26.4%) patients had unnecessary transfusions. Three obstetric patients had immediate minor transfusion reaction. Mean pre-transfusion hemoglobin level of the patients was 8gm/dl (2.8-12.8gm/dl) and post transfusion was 8.4gm/dl (5-12.4gm/dl).

The goal of our study was to inquire about as to whether departmental guidelines for blood transfusion are followed or not, the stratum of personal who will make decision to transfuse blood and blood products and to inquire whether transfusion was based on which hemoglobin level or with expected blood loss more than one thousand ml or hematocrit level of 28 % ± 2 and to seek whether red cell concentrates were being transfused or not and lastly about formal lecture delivered related to blood transfusion in the department. As inferred from above stated risks and the soaring importance attributed to safe blood transfusion, we conducted a study in this regards keeping in sight goals whereby health care professionals from surgical and allied specialties of teaching hospitals of Islamabad and Rawalpindi, were put forward a questionnaire Performa.

MATERIALS AND METHODS

After approval of hospital ethical committee, we carried out a cross-sectional study in the teaching hospitals of Islamabad and Rawalpindi, between Oct, 2007 to Dec, 2007, whereby a total of seventy six health care professionals from surgical and allied specialties by convenient sampling were put forward a questionnaire Performa relating to as to whether departmental guidelines for blood transfusion are followed or not. Question was asked to three personals level i.e. consultants, trainees and medical officers having experience of at least three years in that specialty and a junior resident /house surgeons to negate the subjective bias in their answers. The answers for each department were kept strictly confidential. Data was compared and analyzed by SPSSv19.

RESULTS

A total number of seventy six doctors were surveyed, that included twenty one consultants, twenty nine medical officers/senior post-graduate students and twenty six junior doctors, out of which 52.63 % i.e. forty health care professionals affirmed that they follow the guidelines for blood transfusion and 47.37% i.e. thirty six professionals were lacking the proper follow-up of protocols for blood transfusion. So a high percentage of surveyed participants were not complying with protocols for blood transfusion. The study result breakup is shown in Table-1.

The major indication for blood transfusion in our study was a hemoglobin level of 9g/dl with expected blood loss of more than one thousand milliliters and hemoglobin value was taken into consideration as a guide for further blood transfusion. Furthermore in our study red cell concentrates were transfused in all cases. The hematocrit value stated was 28% for elective surgical cases.

In elective cases consultant/senior registrar decided about blood and blood products transfusion while in emergency on call senior registrar/post-graduate trainee were the personals involved.

The standing operating protocols as regards to safe transfusion of blood and blood products did exist in the respective Hematology Departments of the various teaching hospitals in the study.

Table No. 1: Results

Follow-up of protocols for Blood transfusion	Yes	No
Junior Postgraduate	11	15
Senior M.O/PG	18	11
Consultant	11	10
Total	40	36

DISCUSSION

Tissue oxygenation requires that oxygen supply be matched with oxygen needs, only when the capacity of compensatory mechanisms to anemia are exhausted, that, hypoxia and subsequent tissue injury occur. In our study improvement of oxygen carrying capacity of

blood was the main reason to transfuse packed cells and blood component therapy was mainly to treat disseminated intravascular coagulation state and to pre-operatively correct clotting profile derangements. In study of survey of blood transfusion done by Zafar N[8] a questionnaire was distributed among the surgeons and anesthetists of various hospitals in Lahore. It was found that majority think if the pre-operative hemoglobin is above 10 g/dl blood should not be transfused, even if the anticipated blood loss is between 500-1000 ml. Post-operatively blood should not be transfused, if the hemoglobin is above 9g/dl without any active bleeding. Allergic reactions was the most common side effect of blood transfusion, followed by infection, while only few had mentioned the immuno-modulatory effects of blood transfusion. Fifty percent thought that the transfusion, if necessary, should be packed cells. In our study a hemoglobin level value of 9 gm/dl with expected blood loss about thousand ml was followed by the health care professionals and packed cells were transfused as replacement of blood loss rather than whole blood.

In the study done by Bhattacharya P and colleagues[9] designed to analyze the incidence and spectrum of adverse effects of blood transfusion so as to initiate measures to minimize risks and improve overall transfusion safety in the institute. Analysis of transfusion-related adverse outcomes is essential for improving safety. Factors such as improvement of blood storage conditions outside the blood bank, improvement in cross-matching techniques, careful donor screening, and adherence to good manufacturing practices while component preparation, bedside monitoring of transfusion, and documentation of adverse events will help in reducing transfusion-related morbidity and mortality. The blood transfused in 52.63% of cases in our study did harmonize with the departmental operating protocols.

Anesthetists are more frequently involved in transfusion of blood and blood products to the patients[1], therefore in our study surgical and allied specialties were surveyed. A retrospective study done by Parveen S and colleagues[10] on blood component therapy showed that pregnancy and its complications were the commonest indications for transfusion of blood. Whole blood was given to 898 cases (68.6%). Red cell concentrates were given to 241 cases (18.4%). Fresh frozen plasma/single donor plasma was given to 141 cases (10.7%). Platelets were given to 30 cases (2.3%). Leukocyte depleted blood was given to 4 cases (0.3%). Only three non-hemolytic febrile transfusion reactions were noted in patients who were transfused whole blood and thus with modern facilities blood components can easily be prepared and their appropriate use can decrease morbidity and mortality. In our study packed cells were transfused in all cases. In study done by Nazli Hossain and colleagues[11], the percentage of blood and blood products transfusion in postpartum hemorrhage cases was noted to be 1.6% with mean blood loss being 1088ml (±584ml).

As per SHOT (Serious hazards of transfusion) initiative in UK.[2] analysis of first two annual reports indicate that, 366 cases were reported, of which 191 (52%) were ' Wrong blood to patient 'episodes. There were 22 deaths from all causes including those from ABO incompatibility. There were 12 infections, four bacterial (one fatal), seven viral & one fatal case of malari[12]. Johnson JL and colleagues[13] in their study regarding effect of blood products transfusion stated that regardless of the units of red cell concentrates transfused, fresh frozen plasma transfusion was independently associated with the development of post injury multiple organ failure while platelet transfusion was not associated. Eder AF and colleagues[14] in their study done on complications of blood transfusion reported the overall rate of major complications was 7.4, 5.2, and 3.3 per 10,000 collections for whole blood, apheresis platelets, and automated red cells procedures, respectively.

Among the surveyed healthcare professionals 47.37% i.e. thirty-six personals who are involved in blood transfusion were not fully following protocols for transfusion of blood in our study. In study done by Luby S and colleagues[15] on evaluation of blood bank practices in 2006 they observed that only 8% of facilities asked donors about injecting drug use, and none asked donors any questions about high-risk sexual behavior. While 95% of blood banks had appropriate equipment and reagents to screen for hepatitis B, only 55% could screen for HIV and 23% for hepatitis C.Thus appropriate protocols should be strictly followed for safe blood transfusion. In study done by Abu-Salem and colleagues[16] regarding blood transfusion in obstetrics, stated that 41% of the participants were aware of the possible need for blood transfusion in pregnancy and 88% of all women would accept blood transfusion when necessary. The remaining 12% would refuse blood transfusion, even if it was life-saving, because of the fear of blood transfusion complications.

In data taken from record registers of blood banks of the hospitals namely, Pakistan Institute of Medical Sciences, Islamabad, showed that a total of 17323 units of blood and blood products were issued during the

year 2006 whereas these figures rose to 20840 for the year 2007, up till Nov 11, 2007, while the blood bank of Holy Family Hospital, Rawalpindi, issued 6419 units of blood during the year 2007, and 8763 units of blood were issued by Benazir Bhutto Hospital, Rawalpindi in the same year. The study done by Keating EM and colleagues[17] suggested in their study that in order to avoid the risk of viral infection and immunosuppression and cost of blood transfusion the informed selection of alternatives based on preoperative assessment of hematologic status, estimated blood loss, and hence strategies like preoperative autologous blood collection, the use of haemostatic agents, perioperative blood salvage, and the use of recombinant human erythropoietin (epoetin alfa) to stimulate erythropoiesis can contribute to decreased use of allogenic blood services may enhance blood management practices in major elective surgeries.

An audit study done by Khan FA and colleagues[18] for estimation of blood loss during cesarean, a total of 215 units were cross-matched for 126 patients undergoing Caesarean section delivery.9.5% of cases were transfused intraoperatively and 5.5% post-operatively. The average blood loss estimated by anesthetists and obstetricians was about 498 + 176 ml and 592 + 222 ml respectively. The calculated blood loss based on patients blood volume and drop in hematocrit was 787 + 519 ml while the cross-match transfusion ratio was 9.7. Conclusion drawn was that only 13% of the patients needed blood transfusion. They also recommended that the practice of routine cross-match practice prior to Caesarean section should be re-looked by institutions dealing with obstetric anesthesia.

Chawla T and colleagues[19] in their audit report as regard to blood cross-matching practices at Agha Khan University Hospital examined studied cross-matched to transfused ratio and Transfusion Index as a measure of the efficiency of blood ordering practice and it should ideally be between 2 and 2.5.Data was analyzed for 32 elective surgical procedures in 2131 patients. Majority (2079) (97.56%) of the patients had cross-matched to transfused ratios higher than 2.5. Only 12 in 450 (21.11%) patients, had a Transfusion Index higher than 0.5. There were 13 procedures in which both cross-matched to transfused ratio was greater than 2.5 and transfusion Index less than or equal to 0.5. They concluded that in vast majority of elective surgical procedures routine cross match was not required.

Lastly, infectious complications are also worth mentioning like viral, in the form of hepatitis B, C, HIV(Human Immunodeficiency virus), CMV (Cytomegalovirus) and HTLV type1(human T-cell lymphotropic virus). Parasitic and bacterial complications, of real concern, include malaria, syphilis and Yesinia enterocolitica as described by Triple MA and colleagues[20].Multivariate analysis, in UK, showed that red cell concentrates are an independent risk factor for development of infections.[1]

The study done by Grotte O and colleagues[21] address key issues of transfusions of red blood cells and plasma products in the acute control of bleeding in traumatized patients stated that 30-40% of trauma mortality is attributable to hemorrhage. Timely transfusion of red blood cells and plasma products becomes essential to restore tissue oxygenation, support perfusion, and maintain the pool of active haemostatic factors.

CONCLUSION

Blood transfusion should be treated as an ORGAN TRANSPLANT, like any other organ transplant and it is crucial to increase awareness about it, not only among the health care professionals but also among the general public. Written guidelines for blood transfusion should be followed in each department to ensure patient safety. The use of red cell concentrates should be emphasized in place of whole blood, as many plasma factors are not available and secondly separation into components permits a single donation to meet the individual needs of more than several patients. Lectures on proper guidelines for blood transfusion should be held regularly. The study conducted by us had few reservations that it was not on large national scale, which demand full scale review to address the problem fully.

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Original Article

Organophosphate and Pyrethroid Residues in the Milk of Women and Breast Cancer Patients from Karachi

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ABSTRACT

Aim: The aim of this study was to determine the presence of pesticide residues organophosphate and pyrethroid in the milk of women and in serum of breast cancer patients from different localities of Karachi due to pesticide exposure.

Study Design: An experimental study.

Place and Duration of Study: This is a research-based study that was conducted in the Department of Pharmacology, Institute of Pharmaceutical Sciences, Baqai Medical University, Karachi from March 2008 to March 2010.

Materials and Methods: A total 40 milk samples were collected from private clinics and 6 serum samples from breast cancer patients were also collected from private cancer hospitals based at different areas of Karachi. All the samples were analyzed for the presence of pesticide residues. Samples of milk and serum were prepared accordingly and the purified samples were injected into the HPLC apparatus. The peaks of the samples were compared by the retention time of the standard peaks. The chromatogram obtained indicated the quantity of pesticide residues.

Results: Milk samples and serum samples were analyzed using HPLC technique. Pesticides such as malathion, permethrin, deltamethrin and Polytrin-C were detected in different concentrations. The levels were significantly higher than the maximum residual limit.

Conclusion: It is concluded that the presence of pesticides in the human body is a major concern in the development of various ailments because of possible immunotoxic, mutagenic and carcinogenic potential of pesticides.

Keywords: Organophosphates, Pyrethroids, Human Milk, Breast Cancer, Pesticide Residues.

INTRODUCTION

Pesticides comprises of various chemicals that are deliberately added in the environment for the purpose of eliminating different pests. The main consumption of pesticides is in the agriculture field. In Pakistan large number of populations used synthetic pesticides to save their products. These synthetic pesticides are causing various problems e.g., pesticidal pollution, resistance in pests and accumulation of pesticide residues in the body of animals and human beings. The use of pesticides at one side is important in eliminating the pests but on the other hand produce risk to the human health when used indiscriminately without any proper apparel. Many researchers have reported that the presence of pesticides in the samples of human body fluids and tissues is a major concern from the health point of view because of immunotoxic, carcinogenic and mutagenic nature of the pesticides.

The purpose of this study was to determine and quantify the different pesticide residues in human milk and serum samples of breast cancer patients from different hospitals and clinics of Karachi. The genotoxic or clastogenic potency of lactational exposures to DDT and HCHs in infants described that the frequencies of SCE control and SCEANF showed increasing and decreasing tendencies with the increasing exposure to DDT and also HCHs through the breast milk[1]. The lactational transfer of presumed carcinogenic and teratogenic organochlorine compounds within the first six months of life explained that these compounds are prenatally transmitted from mother to fetus and mother's milk due to its high lipid content[2]. The simultaneous presence of DDT and pyrethroid residues in human breast milk from three town of South Africa for malaria control program has also been reported[3]. It is also indicated that the environmental contamination with organochlorine pesticides may be related to the risk of breast cancer in rural Victoria, Australia and in this respect no significant correlation was noticed between organochlorine contamination and the age-standardized rate of breast cancer across all the regions of Victoria, Australia[4]. Activation and proliferation of breast cancer tumor by estrogenic microenvironment generated by organochlorine residues in adipose tissues adjacent to breast carcinoma may be affected[5]. The high levels of organochlorines in mother's milk from Chennai city, India indicated that the children are at a higher health risk in this city as these chemicals may transfer from

mother's milk through feeding[6]. Human milk of mother living in Northern Tunisia has been assessed for organophosphate residues and found that the concentration of OCPs increased with mother's age and decreased with the number of children[7]. Keeping the hazardous effects in priority, present work was under taken into consideration from the persons of different areas of Karachi. These females are living in highly polluted areas. As pesticides accumulated via food chain, these persons are not adopting precautionary measures in handling the pesticides or misuse of pesticides without knowing their adverse effects and so their health may be affected. Therefore, it is suggested that persons living in the highly polluted areas should be well informed and educated by the controlling authorities not to use synthetic pesticides but encourage them to use phytopesticides. This is the main aim of the present study.

MATERIALS AND METHODS

Selection of Stations: Milk samples were collected from a private maternity clinic located in Shireen Jinnah colony present in the rural area of Gadap, which is approximately 1.5 km far from Baqai Medical University, Fatima Hospital based at Baqai Medical University and a few samples were collected randomly from different areas of Karachi. Serum samples of breast cancer patients were also collected form a private cancer hospital of Karachi.

Collection and storage of sample: Human milk samples i.e., 2-4 ml and 1 ml serum sample from breast cancer patients were also collected in glass vials from different hospitals. All the samples were kept in freezer for analysis.

Pesticide determination: The milk and serum samples were subjected to fat extraction method[10]. The process of sorption was conducted in chromatographic column of alumina[10] and silica[11]. The processed extract was evaporated by placing on a shelf without cover to obtain 1 ml of sample. Pesticide residues in the samples were determined by using high performance liquid chromatography (HPLC) technique. A packed column (Zorbax NH_2) a polar bound phase with particle size of about 7 micrometer in diameter. A mobile phase n-Hexane was used with a flow rate of 1 ml/min. A UV detector was set at 250 nm, pressure at 200 kg/ cm2 and absorbance was 0.32 with chart speed 2.5 mm/min. All these parameters were set on HPLC apparatus Shimadzu SPD – 10A VP detector attached with a chart recorder to obtain the chromatogram of the samples.

Samples of Permethrin and Monocrotophos were run on the apparatus. Chromatograms of DDT, Polytrin-C, Deltamethrin, Malathion, Diazinon, Cypermethrin were run under exact same conditions on HPLC. Samples of milk and serum were prepared accordingly and then 20ul of purified sample was injected in the HPLC apparatus. The peaks were compared on the basis of retention time (RT) with the standard peaks. The chromatograms indicated the quantity of pesticide residues in the samples.

The data was statistically analyzed using the formula:

$$T = \frac{\bar{X} - u_0}{\frac{S}{\sqrt{n}}}$$

RESULTS

A total of 40 milk and 6 serum (from breast cancer patients) samples were analyzed. Five serum samples were found to contain organophosphates, sumithion / malathion, while pyretheriod, permethrin was detected in one sample. The serum sample of Zohra Bibi was found to contain sumithion in a concentration of 56.644 µg / 20µl and 65.2972 µg / 20µl, respectively. Serum samples of Tasleem and Saria were found to contain sumithion in a concentration of 92.6293 and 79.6739 µg / 20µl. Serum sample of Najia was found to contain permethrin in a concentration of 50.6494 µg / 20µl (Table 1A).

The analysed milk samples were found to be contaminated with organophosphates, possibly malathion and pyrethriods, permethrin and deltamethrin. Polyttrin-C was detected only in one sample. Malathion was detected in 57.5% of samples while permethrin was detected in 17.5% of samples. The detected levels were higher than the maximum residual limit (MRL) which is 2 ppm for permethrin, 8 ppm for malathion and 1 ppm for deltamethrin. The magnitude of levels higher than the MRL is indicated in Table 1B. Out of 8 milk samples that showed presence of permethrin, 5 samples were collected from Gadap and surroundings while 2 samples were from Kachi Para and Gulshan. The highest level of permethrin i.e., 100 µg/µl was detected in the milk sample of Arzoo from Gadap which was 98 times higher than the MRL (Table 1B). The mean concentration of permethrin was 58.65 µg/20µl. Polytrin-C was detected in the milk sample of Shamsad from Shireen Jinnah colony. Milk samples of Fozia, Farzana, Noor Jehan and Parveen from Karachi showed no pesticide, while milk sample of Hikmat from Gadap also showed no pesticide residue (Table. 1B). Milk sample of Bano Ghaffar from Kemari was found to contain deltametrin and malathion in a concentration of 64.4451 µg/20µl and 18.9312 µg/20µl respectively (Table. 1B).

DISCUSSION

The highest concentration of sumithion was detected in milk sample of Rehmat from Gadap which was 5375 µg/20µl.The milk sample of Hafiza also showed sumithion 99. 5375 µg/10µl while Gul from north Nazimabad showed 99.8888 µg/10µl of malathion. Presence of malathion in more than half of the samples is probably due to the extensive use in Gadap by

Table 1A: Quantification of pesticide residues in serum of breast cancer patients.

Sample no.	Name	R.T.	Pesticide detected	Conc. in µg/20µl
106	Najia	3.007	Permethrin	50.6494
995	Saba	3.189	Malathion	72.4077
107	Tasleem	3.343	Malathion	92.6293
47	Saira	3.322	Malathion	79.6739
998	Kulsoom	3.185	Malathion	65.2972
44	Zohra Bibi	3.478	Malathion	56.6445

Table1B: Quantification of pesticide residues in milk of women residing in Gadap and different areas of Karachi.

Name	Age	Location	Pesticide Detected	R.T.	Conc. In µg/20µl	No. of times higher than MRL.
Khayaloo	35	Mahajir camp	Sumithion	3.316	58.7284	50.7284
Mehboba	30	Gadap	Sumithion	3.252	53.5354	45.5354
Ana Noran	40	Gulgoth	Permethrin	3.048	41.0629	39.0629
Arzoo	27	Gadap	Permethrin	3.020	100	98
Dhani	28	Gadap	Permethrin	3.041	37.2330	35.2330
Nazar	26	Mahajir camp	Sumithion	3.225	85.9060	77.906
Resham	25	Gadap	Sumithion	3.298	99.9113	91.9113
Monis	26	Gadap	Sumithion	3.143	74.9368	66.9368
Asia	30	Zakaria Goth	Permethrin	2.970	98.5946	96.5946
Nazeema	25	New sabzi mandi	Permethrin	3.068	77.4295	75.4295
Hikmat 1	40	Gulgoth	Sumithion	3.267	64.5155	56.5155
Shahzadi	20	Gadap	Permethrin	3.040	64.2696	62.2696
Ghousia	26	Gadap	Sumithion	3.234	97.7971	89.7971
Atiya	21	Gadap	Sumithion	3.234	97.7971	91.6028
Hafiza	26	Gadap	Sumithion	3.240	99.5375	91.5375
Rehmat	25	Gulgoth	Sumithion	3.240	99.5375	91.9785
Bachandi	28	Gadap	Sumithion	3.224	99.0778	91.0778
Mahiyat	27	Gadap	Sumithion	3.197	73.0627	65.0627
Asma	23	Gadap	Sumithion	3.170	99.9589	91.9589
Sakina	29	Sohrab Goth	Malathion	3.125	52.672	44.6728
Bano Ghaffar	30	Kemari	Deltamethrin	2.683	64.4451	63.4451
			Sumithion	3.516	18.9312	10.9312
Shama	26	Gulshan	Permethrin	2.983	39.0845	37.0845
Noor Jehan	26	Gulshan	----------	-------	----------	
Gul	30	N.Nazimabad	Malathion	3.304	99.8888	91.8888
Ayesha	27	Gulshan	Malathion	3.288	79.8140	71.814
Meharunnisa	27	Gulshan	Malathion	3.336	67.6931	59.6931
Chand Bano	33	Gulshan	Malathion	3.192	79.5629	71.5629
Tahira	25	Kachi para, Shireen	Permethrin	2.971	51.4999	49.4999
Urooj	28	Jinnah colong	Malathion	3.161	75.2820	67.282
Fozia	30	N. Nazimabad	----------	-------	----------	
Farkhunda	24	Mehmar camp	----------	-------	----------	
Fozia		Shireen Jinnah				
		colony				
Perveen	25	Masood road	----------	-------	--------	
Shamshad	25	Shireen Jinnah	Polytrin-C			
		colony	a.Prophenophos b. Cypermethrin	a.2.445 b.3.389	a.21.3055 b.73.5890	

farmers and also because it was used in Karachi for 10 years in the antimalarial campaign. Even though malathion is an insecticide of relatively low toxicity, and its presence in the maternal milk is a serious

concern. Same situation is for the presence of permethrin and deltamethrin and Polytrin-C. The p-value of Sumithrion/ Malathion in milk samples was 0.0001 and the p-value for Sumithion/ Malathion in serum samples of breast cancer patients was also 0.0001. Therefore the levels of Sumithion/ Malathion are significantly high. There are several case-control studies reported by some researchers that associate parental exposure to pesticides or pesticide use in the home with childhood brain tumors, lymphomas leukemias, testicular cancers, and in human milk as well as for possible correlation e.g.,. An association of acute nonlymphoblastic leukemia risk has been correlated with pesticide exposure. Association between childhood cancer has also been correlated with the exposure of organophosphate pesticide. The same findings have also been noticed by the present study. Exposure to estrogen throughout a women's life is a risk factor for the development of breast cancer[5]. Similarly Environmental contamination data derived from the breast milk with the exposure of pesticides causes the development of breast cancer[4]. This is almost in line with the findings of the present study. Presence of pesticide residues in human milk like persistent organochlorine, PCDDs, PCDFs and dioxin-like PCBs levels has been reported by many researchers[7,14,15]. The present study also determined the levels of pesticide residues but particularly investigated the levels of organophosphate and pyrethroid residues such as sumithion, malathion, permethrin and deltamethrin in the human breast milk and serum samples of breast cancer patients collected from different areas of Karachi, Pakistan.

CONCLUSION

In view of the analysed milk sample data, it is concluded that the milk samples were found to be contaminated with organophosphate particularly the presence of malathion and pyrethroid residues. It has also been noticed that the most frequently detected pesticides are the malathion / sumithion and the detected levels were higher than the maximum residual limit which is particularly seen in case of malathion. As malathion is an insecticide of relatively low toxicity, so its presence in the mother's milk is alarming. Therefore, through this study it is suggested that the pesticide controlling authority should provide the knowledge to the population about this serious situation.

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Original Article

The Role of Allopurinol and Angiotensin Receptor Blockers in Serum Uric Acid Reduction in Gouty and Hypertensive Patients

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ABSTRACT

0bjective: To evaluate the effect of Allopurinol in combination with angiotensin receptor blockers on hyperuricemia in gouty and hypertensive patients.

Study design: Randomized, open label, prospective, comparative trial.

Place and Duration of Study: This study was conducted in the Department of Pharmacology. &Therapeutics; BMSI/JPMC, Karachi from April 2010 to November 2010.

Materials and Methods: 80 hypertensive and hyperuricemic patients were enrolled from OPD and medical wards and were divided into two groups. group DR-1(40 Patients) were given allopurinol 300mg plus candisartan 8mg daily and group DR-2 (40 patients) were given allopurinol 200mg Plus Losartan 50mg, daily four 4 months. 6 patients were unable to continue the follow-up 3 patients in each group.

Results: DR-1combination therapy decreased serum uric acid level from 8.92 ± 0.19mg/dl at day 0 to 5.33 ± 0.11mg/dl at day120. DR-2 group also showed a significant reduction in serum uric acid level from 9.14. ± 0.19mg/dl at day 0 to 4.74 ± 0.09mg/dl at day 120 ($p < 0.001$). when effects were compared in both treatment groups, the effect of group 2 regimens on serum uric acid level was more marked due to Losartan combination which also have uricosuric effects than in group 1 regimen, with average percentage decrease in serum uric acid -40.35% in group DR-1 and -48.24% in group DR-2.

Conclusion: The allopurinol 200mg and Losartan 50mg is more effective than allopurinol 300mg+ candesartan 8mg, to decrease serum uric acid level and group DR-2 drugs combination useful in those hyperuricemic patients who cannot tolerate high doses of uric acid lowering drugs.

Key Words: Hyperuricemia, allopurinol, Losartan Potassium, Serum uric Acid.

INTRODUCTION

Hyperuricemia is a metabolic disease that has become quite common over the past several decades. Hyperuricemia causes gouty tophi, gouty arthritis, nephropathy caused by uric acid and uric acid kidney stones .[7] Hyperuricemia with or without gout is associated with cardiovascular disease including stroke, peripheral vascular disease and coronary diseases .[1]

Hyperuricemia is commonly found in 25% untreated hypertensive patients, 50% patients on diuretic therapy and in >75% malignant hypertensive patients .[2] Various mechanisms suggested the importance of increase serum uric acid levels in cardiovascular diseases as a direct causative agent. Hyperuricemia cause endothelial dysfunction and impaired oxidative metabolism. It also causes platelet adhesiveness and aggregation .[3]

Increased serum uric acid is a causative agent to predict stroke and excess mortality in patients of non insulin-dependent diabetes mellitus.[5] In elderly population there is independent association between hyperuricemia and increased incidence of fatal stroke. Hyperuricemia in diabetic patients, along with obesity, insulin resistance and blood pressure plays a crucial role in the metabolic syndrome which in turn causes endothelial dysfunction.[6]

Allopurionl is the main drug which inhibit xanthine oxidase the enzyme convert xanthine into uric acid.[9] In human proximal brush border membrane tubular secretion and reabsorption of urate are mediated by urate/anion exchanger and urate voltage-sensitive transporter.[10] Losartan inhibits the urate/ anion exchanger and urate/chloride exchanger in the renal proximal brush border membrane .[12] Losartan potassium prevent renal stone formation by increase urinary PH , which intern prevent supersaturation and increase the solubility of uric acid.[11]

MATERIALS AND METHODS

This study was conducted at the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Centre (JPMC) Karachi from April 2010 to November 2010**;** eighty gouty and hypertensive patients with hyperuricemia were enrolled in the study, selected from Orthopedic and Medical OPDs of Jinnah Postgraduate Medical Centre (JPMC) Karachi and divided into two groups. The 74 patients remained associated through out the study period, Whereas 6 patients were dropped due to failure of the follow-up period among those 3 patients in Allopurinol 300mg + Candesartan 8mg group(DR-1) and 3 patients in

Allopurinol 200mg + Losartan 50mg group (DR-2). Gouty patients of either sex ages from 35 to 65 years having hyperuricemia and hypertension with serum uric acid level between 7.0 mg/dl to 12.0 mg/dl where included in the study. Lactating and pregnant women, subjects with cerebrovascular accidents or transients ischemic attacks within past three years, Secondary hypertension, Cardiac arrhythmia, Renal urolithiasis, Angina pectoris, hepatic and renal impairment and drugs which can affect serum uric acid level and urinary uric were excluded. . Combination therapies were given for 120 days daily and routine diet was advised. To estimate serum uric acid blood sample (3 ml) of each patient were drawn on day-0 and at every month follow up visits. Uric acid was estimated by the enzymatic colorimetric method.

Statistical software SPSS version 13 was used for data feeding and analysis, t. test was used to compare mean and standard deviation of quantitative variable between the two groups. The statistical significance of difference between the mean values of the two groups was evaluated by student t test.

Comparison of the effect of the two treatments groups was evaluated by paired t test. $P < 0.05$ and $P < 0.001$ were considered as statistically as significant and highly significant. At the end of study the percentage variation in serum uric acid level 0 to day 120 was calculated in both treatment groups separately by the following formula

$$\frac{\text{Day 0} - \text{Day 120}}{\text{Day 0}} \times 100$$

RESULTS

The enrolled patients were 67% male and 33% female. The Mean age of male patients were 52 years and the mean age of female patients were 49 years.

Patients given allopurinol 300 mg and candesartan 8 mg for 120 days revealed overall decrease in mean serum uric acid levels. The decrease in serum uric acid level was highly significant on day 30 i.e. 6.87± 0.12 mg/dl, as compared to 8.92 ± 0.19 mg/dl on day 0.

Mean serum uric acid levels further decrease to 6.18 ± 0.09 and 5.75 ± 0.11 mg/dl on day 60 and day 90 respectively, which were also highly significant. The serum uric acid levels were decreased to 5.33 ± 0.11 mg/dl on day 120. When compared from day 0 to day 120 the total reduction in serum uric acid level was 3.56 ± 0.13mg/dl which was highly significant, with overall reduction of 40.24%.

Patients given allopurinol 200 mg and losartan 50 mg for 120 days revealed overall decrease in mean serum uric acid levels. The decrease in serum uric acid level was highly significant on day 30 i.e. 6.54 ± 0.10 mg/dl, as compared to 9.14 ± 0.19 mg/dl on day 0.

Mean serum uric acid levels further decreased to 5.82 ± 0.09 and 5.27± 0.09mg/dl on day 60 and day 90 respectively, which were also highly significant. The serum uric acid levels were decreased to 4.74 ± 0.09 mg/dl on day 120. When compared from day 0 to day 120 the total reduction in serum uric acid level was 4.41 ± 0.14mg/dl which was highly significant, with overall reduction of 48.14 %.

Table No.1: Changes in Mean Serum Uric Acid level following Treatment with Drugs in Group Dr -1 and Dr- 2

Groups	Serum uric acid concentration mg/dl from days 0 to 120					% Decrease
	0	30	60	90	120	
DR-1	8.92± 0.19	6.87±0.12**	6.18±0.09**	5.75±0.11**	5.33±0.11**	40.32
DR-2	9.14± 0.19	6.54± 0.10**	5.82± 0.09**	5.27± 0.09**	4.74± 0.09**	48.14

DR-1 = Allopurinol 300 mg + Candesartan 8 mg

DR-2 = Allopurinol 200 mg + Losartan 50 mg

**P < 0.001 highly significant as compared to day 0

Figures are in (Mean ± SEM), n=40 (day 0), n=37 (day 30 to 120)

DISCUSSION

This study demonstrates significant change in serum uric acid as a result of administration of allopurinol 300mg in combination of candesartan 8mg (DR-1), and Allopurinol 200mg in combination with Losartan 50mg (DR-2) daily for four months. In our study drugs of both groups were well tolerated and effectively reduce serum uric acid but DR-2 drugs was more effective. Warzner and his colleague have evaluated the effect of Losartan on serum uric acid in hypertensive patients with hyperuricemia and gout, it was shown that Losartan significant decrease in serum uric acid level (p <0.01) in patients with hypertension, elevated levels of serum uric acid and gout. They found that increasing the dose of Losartan from 50mg once daily to twice a day did not further reduce serum uric acid level .[14] Where as in our study the combination therapies were given which were more effective to decrease serum uric acid level. Allopurinol after 24 month treatment in hyperuricemic patients was significantly decreased serum uric acid level (P= 0.001)[8].Where as in our study we add in DR-1 candesartan and losartan in DR-2 to allopurinol. The reduction in serum uric acid levels by

both combination therapies were more pronunced as compare to marium study may be due to allopurinol block uric acid synthesis and losartan increase its renal excretion. The administered dose of allopurinol was more 300mg/day in DR-1 as compare to 200mg/day in DR-2 but due to addition of losartan 50mg/day in DR-2 the serum uric acid reduction efficacy were equal in both groups. Losartan and benzbromazone 11% decrease in serum uric acid level in combination therapy.[4]

Losartan decreases serum uric acid level by 20-25% if used alone.[12],[14] In our study Allopurinol 300mg + Candisartan 8mg combination therapy decreases serum uric acid level by 40.35% and Allopurinol 200mg + Losartan 50mg combination therapy decreased serum uric acid by 48.24%. The use of low dose combination therapy is associated with a fewer side effects than higher doses of single agent required to achieve same levels. However patients on combination therapies showed more pronounced reduction in serum uric acid level and the tolerance generally good with no side effects.[13]

CONCLUSION

In present study allopurinol 200 mg + Losartan 50 mg was found to be more effective than allopurinol 300 mg + Candesartan 8 mg in reducing serum uric acid level.

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Original Article

Evaluation of Efficacy of Budesonide in Prevention of Cardiovascular Risks in Chronic Obstructive Pulmonary Disease Patients

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ABSTRACT

Background: Cardiovascular disease is a major cause of mortality and morbidity in COPD patients. Systemic inflammation plays a major role in the pathogenesis of cardiovascular disease in COPD. It has, therefore, been suggested that anti-inflammatory agents may prevent cardiovascular disease. it would be plausible that inhaled steroids, such as Budesonide, reduce the local inflammation and subsequent cardiovascular morbidity, thus a local effect on the lung resulting in diminished spill-over of inflammation systemically to the cardiovascular system is an attractive hypothesis.

Objective: To assess the impact of Budesonide in reducing the cardiovascular risk in COPD patients**.**

Study Design: Experimental Randomized Study.

Place and Duration of Study: This study was conducted in the Department of Pharmacology and Therapeutic, Basic Medical Sciences Institute, JPMC Karachi in collaboration with Department of chest medicine, JPMC, Karachi from Dec. 2010 to March, 2011.

Materials and Methods: Thirty five patients with moderate stable COPD, with hsCRP level >3mg/lit, were evaluated in an open label, intention to treat clinical trial. The patients were assigned to give Budesonide (Pulmicort) inhaler 200mcg BD for 12 consecutive weeks. The primary study outcome was to evaluate the reduction in cardiovascular risk by evaluating the improvement in FEV1 and reduction in hsCRP levels, was evaluated at day 30, 60 and day 90.

Results: Thirty four (96%) patients were completed the study. At baseline hsCRP levels was 6.68±0.26 which decrease to 5.82±0.20 (P<0.010) at day 90. FEV1(L) at baseline was 2.12±0.05 and at day 90 FEV1 increased upto 2.40±0.04 (P<0.001). This shows that, the Budesonide can statistically significant decrease the hsCRP levels and increase the FEV1.

Conclusion: In conclusion, Budesonide effectively decrease the cardiovascular risk by decreasing the systemic inflammation which were indicated by decreasing the hsCRP levels and also improve pulmonary functional capacity in COPD patients.

Key Words: COPD, Budesonide, Pulmicort, hsCRP, FEV1, CVD,ICS.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a syndrome of chronic progressive airflow limitation which occurs as a result of chronic inflammation of the airways and lung parenchyma, and is at most partially reversible[1]. The abnormal inflammatory response found in COPD appears to be an amplification of the normal inflammatory response to inhaled noxious agents (cigarette smoke or other irritants) in the susceptible patient. It is characterized by influx of neutrophil into the airway lumen and by increased macrophage and T lymphocyte numbers in the airway wall[2].

COPD is leading cause of death and disability worldwide. The rise in morbidity and mortality from COPD will be most dramatic in Asian and African countries over the next two decades, mostly due to progressive increase in the prevalence of smoking[3].The WHO estimates that 80 million peoples worldwide have moderate to severe COPD with 5% of all death being attributed to the disease[4] WHO estimated that COPD is currently the 12th most common cause of morbidity and the 6th leading cause of death in the world. By 2020 it is estimated to become the 5th most common cause of disability and 3rd most frequent cause of death just behind coronary and cerebrovascular disease[5,6].

Although these figures are alarming, they are likely to be gross underestimates of the true health and economic burden of COPD because COPD is an important risk factor for other causes of morbidity and mortality, including cardiovascular disease[7]. In Pakistan, the estimated COPD mortality rate is 71 deaths per 100,000 and the fourth highest rate among 25 most population in the world[8].

COPD is not longer being considered a disease only of the lungs. It is associated with a wide variety of systemic consequences, most notably increased risk of cardiovascular diseases, depression, osteoporosis and vascular weakness[9].

Systemic inflammation in COPD reflected by elevated CRP levels and impaired pulmonary functions may have additive effects in increasing the risk of cardiac disease[10]. Impaired lung function is a strong predictor of cardiovascular death, both independent of and additive with the risk conferred by smoking. It has also been proposed that coronary artery disease in patients with COPD results in part from spillover of pulmonary derived inflammatory cytokines (e.g. IL-6, TNF-α)[11].

High sensitive C-reactive protein analyses have already been recommended for clinical application in the detection and prevention of cardiovascular disease[12,13]. It has, therefore, been suggested that anti-inflammatory agents may prevent cardiovascular disease[14].

Corticosteroids are effective in reducing airway and systemic inflammation. Budesonide is a new generation glucocorticosteroids with high anti-inflammatory activity and reduced systemic side effects and it is widely used to treat COPD in clinical practice[15].

Thus, it would be plausible that inhaled steroids, such as Budesonide, reduce the local inflammation and subsequent cardiovascular morbidity[16]. In this case, a local effect on the lung resulting in diminished spill-over of inflammation systemically to the cardiovascular system is an attractive hypothesis, since systemic steroids may have a dose–dependent harmful effect on the risk for ischemic heart disease[17].

MATERIALS AND METHODS

Patients: A total of 35 patients having diagnosis of stable moderate COPD met the inclusion criteria were enrolled after taking written and informed consent. Patients of both sexes with moderate COPD as indicated by spirometry assay FEV1 < 80% and FEV1/FVC < 70%, with age ranges between 35-65 years and with hsCRP levels >3mg/lit were included in this study. Patients with unstable COPD, history of exacerbations previous 3 months, patients already on Steroid therapy, or history of oral steroid usage during previous 3months, pregnant or lactating mothers, patients with connective tissue disorders, patients with active or chronic peptic disease and with documented history of active coronary artery disease are excluded from the study.

Study procedure: The study was extended over 12 week's period. During this treatment period patients were assigned to tablet Budesonide (200 µg) 2puffs daily for 12 weeks followed by monthly follow up visits. The rescue medications were allowed SOS during the study.

At baseline pulmonary function test (FEV1, FVC, FEV1/FVC ratio) were performed. Impact of therapy on health related quality of life were assessed by BODE index and SGRQ score and impact of therapy on cardiovascular risk were assessed by changes of FEV1 and hsCRP levels from the baseline which were the primary outcomes of this study. The safety and tolerability of drug was assessed by maintaining adverse events at each follow up visits and performed LFT and creatinine kinase levels at baseline and at end of study.

Statistical Analysis: Statistical software SPSS (statistical Package for Social Sciences) ver 11.5 was used for data feeding and analysis. Clinical characteristics will be summarized in terms of frequencies and percentages for qualitative variables (gender, smoking history, sputum production, family history, etc.) mean ± S.D. for quantitative variables (age, PEFR, FEV1, FVC, FEV1/FVC ratio, Liver function test (LFT), lipid profile, etc). Student t-test (paired) was used for comparison of quantitative data from baseline (day-0) to day-30, day-60 and day-90. In all statistical analysis only p-value <0.05 was considered significant.

RESULTS

35 patients were selected for treatment. One patient withdrew during treatment period and therefore failed to complete the study. Reason for withdrawal was non compliance. Demographic and baseline clinical characteristics are shown in table 1.

Table No.1: Demographic characteristics of enrolled patients

Characteristics	**Group B** (n=34)
Gender	
Male	25 (73.5)
Female	9 (26.5)
Smoking history	26 (75.8)
Cough	25 (73.5)
Sputum production	14 (41.6)
Age (years)	56.8 ± 0.68
Smoking, Pack/year	28.1 ± 1.43
MMRC Dyspnoea score	2.88 ± 0.11
History of exacerbation in last 6 months	1.8 ± 0.11
Peak expiratory flow rate	165 ± 2.01
BMI (Body Mass Index)	19.9 ± 0.35
FEV1	2.12 ± 0.05
FVC	3.1 ± 0.08
FEV1/FVC ratio %	0.60 ± 0.01
History of any comorbodities	
Hypertension	9 (26.5)
Diabetes mellitus	4 (11.)
Stable ischemic heart disease	2 (5.9)
Family history of COPD	15 (44.1)
Family history of ischemic heart disease or hypertension	23 (67.6)

At baseline the mean±SEM of CRP was 6.68±0.26 and FEV1 was 2.12±0.05.

At day 30 the mean±SEM of CRP was 6.50±0.22 and percent change from baseline was 2.7% and p-value from the baseline was statistically non significant (0.599). The mean FEV1 was 2.24±0.05 and p- value from the baseline at day 30 was statistically non significant (0.094).

Table No.2: Assessing the reduction of cardiovascular risks by assessing the C-Reactive protein and forced expiratory level in one second levels (FEV1) with treatment Inhaled Budenoside

Variables	Mean ± SEM (n=34) (% change)	P-value
Reduction in C-reactive protein levels		
Day – 0	6.68 ± 0.26	-
Day – 30	6.50 ± 0.22(2.6%)	0.599
Day – 60	5.97 ± 0.18(10.7%)	0.028 *
Day – 90	5.82 ± 0.20(12.9%)	0.010 **
Improvement in FEV1 levels		
Day – 0	2.12 ± 0.05	-
Day – 30	2.24 ± 0.05(5.7%)	0.094
Day – 60	2.31 ± 0.04(9%)	0.004 **
Day – 90	2.40 ±0.04(14.2%)	0.001 **

- ** p<0.01, * p<0.05 statistically significant from base line (Day-0)
- Percentage change in parenthesis

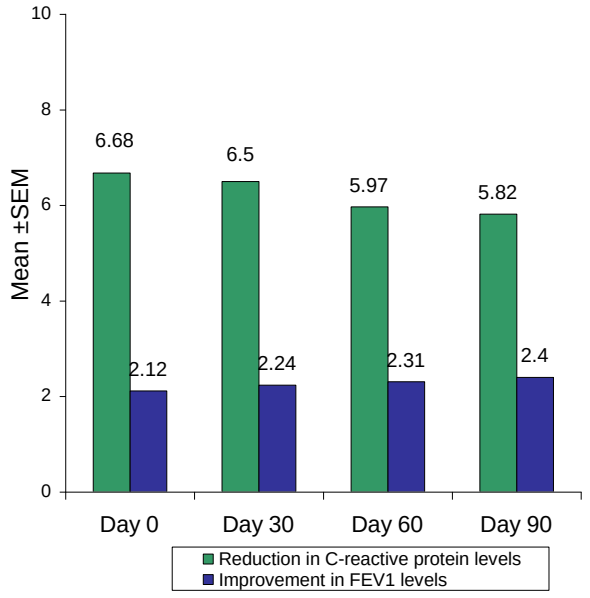

Figure No.1: Assessing the reduction of cardiovascular risks by assessing the C-Reactive protein and forced expiratory level in one second levels (FEV1) with Budesonide treated patients

At day 60 the mean±SEM of CRP was 5.97±0.18 and percent change from baseline was 10.7% and p-value from the baseline was considered statistically significant (0.028). The mean FEV1 was 2.31±0.04 and percent change was 9% and p- value from baseline was statistically highly significant (0.004).

At day 90 the mean±SEM of CRP was 5.82±0.20, percent change from baseline was 12.9% and p-value from the baseline was considered highly significant (0.010). The mean FEV1 was 2.40±0.04 and p-value was considered statistically highly significant (0.001).

DISCUSSION

Coronary artery disease is the most common cause of death in COPD patients, estimated to affect between 20-50%. Reduced FEV1 is a powerful marker for CAD and mortality from CVD. It is striking that reduced FEV1 ranks second only to smoking, just above blood pressure, social class and cholesterol as predictor for CVD related mortality in COOPD patient in both males and female[18].

Melbye et al. shows a strong link between bronchial airflow limitation and the circulating CRP levels in an elderly population. Measuring CRP may be useful part of the diagnostic work up in COPD patients[19].

Glucocorticoids have potent anti-inflammatory effects and therefore are of theoretic benefit in patients with COPD[20]. Furthermore, the anti-atherogenic properties of corticosteroids have been demonstrated in several animal studies[21,22,23].

The beneficial effects of ICS on the risk of acute myocardial infarction may be explained by the anti-inflammatory effects of ICS. Anti-inflammatory actions of corticosteroids involve the modification of the expression of a wide number of genes, in turn, inhibiting the synthesis of cytokines (interleukin (IL)-2, IL-6, tumor necrosis factor -a, interferon-c), adhesion molecules (intercellular adhesion molecule 1, endothelial leukocyte adhesion molecule 1), enzymes (inducible nitric oxide synthase, cyclooxygenase, collagenase) and other proteins (granulocyte-macrophage colony-stimulating factor) involved in inflammation[24], and implicated in the pathogenesis of acute coronary syndromes[25].

In 2004, Sin and colleagues reported that ICS therapy may provide a similar CRP benefit for those patients with respiratory disease. The authors performed a randomized, double-blind, placebo-controlled trial involving 41 patients with mild-to-moderate COPD to examine the effects of ICS therapy on systemic inflammation. The withdrawal of ICS therapy increased baseline CRP levels by 71%, while a return to ICS therapy for 2weeks reduced CRP levels by 50%. No significant changes were observed with placebo. An additional 8 weeks of ICS therapy was associated with CRP levels that were lower than those at baseline (29% reduction).Interestingly, 2 weeks of prednisone therapy reduced CRP levels by a comparable amount (63%) to that of ICS therapy, even though the ICS dosage (fluticasone,500 µg bid) was thought to be too low to

mimic the effects of therapy with systemic corticosteroids[26].

These findings are consistent with a recently published observational study by Pinto-Plata and colleagues, who found that users of inhaled corticosteroids had serum CRP levels that were on average ~40% lower than those among corticosteroid non-users[27].

Huiart L et al, conducted the population based cohort study in mild to moderate COPD patients and found a protective effect of ICS on the risk of AMI for daily medication doses ranging 50–200 mg of beclomethasone or the equivalent. For higher doses of ICS the risk returned to baseline[28].

Analysis of the European Respiratory Society's study on Chronic Obstructive Pulmonary Disease (EUROSCOP); which is a 3-yr, placebo-controlled study of an inhaled corticosteroid Budesonide 800 *µg/day in mild COPD patients.* The results of this study support the hypothesis that treatment with inhaled Budesonide reduces ischaemic cardiac events in patients with mild chronic obstructive pulmonary disease[29].

Inhaled corticosteroids may reduce CRP production indirectly by downregulating the expression of IL-6[30]. Previous studies indicate that IL-6 is a major signaling cytokine for CRP expression by hepatocytes[31]. Importantly persistent therapy with inhaled corticosteroids attenuates IL-6 expression in patients with COPD[32].

Thompson and associates by comparing treatment with inhaled beclomethasone to placebo in a group of subjects with mild chronic bronchitis concluded that inhaled steroid treatment led to significant improvement in spirometry, BAL cellularity, and protein content as compared to placebo, in 50% of the patients[33].

Riancho and colleagues performed a meta-analysis of 12 placebo- controlled trials of ICS in COPD. Short-term studies showed that ICS induced a small increase in FEV1 (mean 96 ml after 1 to 6 months). Longer-term studies indicated that after 1 to 3 years of continued therapy, FEV1 was higher in steroid treated subjects than in control subjects, but only by 51 ml[34]

In conclusion this study demonstrated that the Budesonide (Pulmicort inhaler) effectively decreases the cardiovascular risk by decreasing the systemic inflammation which was indicated by statistically significant decrease in hsCRP levels and decrease in pulmonary component of inflammation was indicated by improvements of pulmonary functional capacity in COPD patients.

CONCLUSION

In conclusion, Budesonide effectively decrease the cardiovascular risk by decreasing the systemic inflammation which were indicated by decreasing the hsCRP levels and also improve pulmonary functional capacity in COPD patients.

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