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Editorial

Daily Exercise Helps Keep the Sniffles Away

Dr. Azhar Masud Bhatti

A. Director Health Services, EPI Punjab, Lahore
&
Editor in Chief

Regular exercise can improve your mood, help you lose weight, and add years to your life. Still need another reason to hit the gym? A new study suggests that working out regularly helps ward off colds and flu.

In the study, researchers followed a group of about 1,000 adults of all ages for 12 weeks during the winter and fall of 2008. During that time, people who logged at least 20 minutes of moderate aerobic exercise such as jogging, hiking, or swimming on five or more days per week were sick with cold or flu symptoms for just five days on average, compared to about 8.5 days among people who exercised one day per week or less.

What's more, regular exercisers tended to have milder symptoms when they were ill. Compared to the people who barely exercised, those who worked out frequently rated their symptoms about 40% less severe overall, according to the study, which was published in the British Journal of Sports Medicine.

Exercise is thought to boost the circulation of the virus fighting white blood cells known as natural killer cells—the “Marine Corps and Army of the immune system,” says the lead author of the study, David Nieman, a Professor of health, leisure, and exercise science at Appalachian State University, in Boone, N.C. “Exercise gets these cells out to deal with the enemy.”

The increased immune activity brought on by exercise only lasts for about three hours, but the cumulative effect seems to keep disciplined exercisers healthier than most. “As the days add up, it adds up to improved protection (from) the viruses that can make you sick,” Nieman says.

Endorphins may also play a role, says Len Horovitz, MD, a pulmonary specialist of Leno Hill Hospital, in New York City. These feel-good neurotransmitters the source of the so called runner's high have “positive effects on the immune system, so it's not surprising there's a spike in immune cells,” says Dr. Horovitz, who was not involved in the study.

It's also possible that people who exercise frequently tend to lead healthy lifestyles in general, and are therefore less likely than couch potatoes to get sick.

Nieman and his colleagues measured a host of factors besides exercise that could potentially affect a person's susceptibility to cold or flu, including age, gender, diet, stress levels, marital status, smoking and educational attainment. Of all of these physical activity was most closely linked to the number of days a person spent

sick, although some characteristics, such as being married and eating a lot of fruit, seemed to help protect against colds and flu as well.

“You can't do much about your age, and you can't do much about your gender. Here's something you can really do,” Nieman says, “Exercise is the most powerful weapon that an individual has in their hand to reduce illness days.”

Exercise is vital to keep a person healthy. Not only does it add to health benefits but also keeps a person fit and young. Fortunately it is something that we all can do and it is never too early and neither too late to make exercise a healthy habit. Sadly, many women with their burdening responsibilities find exercise routine vigorous and time consuming. As work, family and other responsibilities take precedence, they find it difficult to go to the gym or to fit any form of exercises into their schedule. However, aerobic exercise are one such practice that can be done easily at home without the help of an instructor.

Aerobics is a physical exercise that includes stretching and strength training routines of flexibility, muscular strength and cardio-vascular fitness. Practically aerobic exercises stimulate the heart and lung activity by increasing the level of oxygen, strengthening both the circulatory system and physiological endurance. “Aerobic exercises are low in intensity. Due to its rhythmic movements, it is suitable for women, old people and those who are not very fit.

- Strengthens the respiratory system, bones and muscles.
- Strengthens heart muscles.
- Normalises blood pressure.
- Reduces risk in osteoporosis.
- Reduces obesity and helps in weight loss.
- Increases cell respiration by adding to the amount and speed of the blood flow.
- Reduces the dangers of heart diseases.
- Lowers cholesterol.
- Prevents the onset of type 2 diabetes in adults.
- Increases energy level.
- Alleviates anxiety and depression.
- Prevents arthritis.
- Improves the quality of sleep.
- Decreases the risk of various types of cancer.

“if you have a hectic lifestyle that does not allow you to join a gym, you could always workout at home. For that planning is very important, so set a particular time for exercise and plan your weekly routine in advance,” Here are some of the best aerobic exercises:

Dance: It is the most effective way of aerobics that can be done without equipment.

Skipping: this fun exercise is easy and can be done on the spot. Skipping keeps one light on the toes and is also a very efficient fat burner.

Shadow boxing: this is an excellent way to burn calories and tone muscles. It's mostly low impact and can be done in doors.

Aerobics for the young and old: People in their teens are more energetic and can cope up with heavy and fast exercises while older people will find it impossible to keep up with a heavy exercise routine. “To avoid risks and injuries, older people need to follow low impact aerobics while younger people can practice high impact aerobics.”

Low impact aerobics: Low impact exercises are designed to protect the muscle groups from being overused or stressed.

They are for older people, pregnant women or those suffering from diseases like osteoporosis and arthritis. Also those who are completely new to exercise can start off with this routine as they may be at a risk of injury if they start high intensity exercises. Low impact aerobic exercises include walking and stair climbing.

High impact aerobics: High impact exercises are for younger people or those who are used to working out regularly. Such exercise routines are meant to strengthen the muscles and lungs. It also helps in reducing cholesterol levels.

The different types of high impact aerobics include jazz and hip-hop aerobics. Hip-hop aerobics include contemporary dance steps while jazz aerobics include funky twists and some steps of yoga.

Negative affects: Aerobics has many physical and mental health benefits but it can also harm people suffering from a number of health conditions. Aerobics can be dangerous for:

- Those suffering from heart disease.
- People who have recently had a surgery related to the heart, kidney or liver.
- Women who have a weak body immune system.
- Those suffering from arthritis, diabetes, high level of blood pressure, heart diseases, osteoporosis or any other kind of blood diseases.

It is advised to people who suffer from the above mentioned conditions to consult medical experts before starting off with any exercise routine.

Lower back pain can cause people to stop exercising because of discomfort or fear of causing further injury to their back. The lack of activity can cause the back

muscles to become “de-conditioned,” or weakened, setting up conditions for even more chronic pain.

Exercises such as yoga help reserve the muscle weakness by strengthening muscle of the mid-section, including the back extensors, abdominals and gluteus, which are key for stabilizing the trunk and decreasing the load on the spine.

According to background information in the study. Mary Lou Galantino, a professor of physical therapy at Richard Stockton College of New Jersey, said the study confirms previous research about the benefits of yoga for helping with conditions as varied as menopause and osteoarthritis. Other research has shown that yoga can improve mood in women with breast cancer.

“There is so much data excitingly pointing to the physical, psychological and spiritual benefits of yoga,” Galantino said. “I also believe there's a social aspect to yoga. It can foster a sense of community and overarching well-being.

There is integrated care. If done with proper breathing, postures and meditation yoga does all of that. You have to have all of the elements. If we westernize it and make it solely an athletic program, then you may not received all of the benefits.”

Though there are many causes of lower back pain, the culprit is often a herniated disc or arthritis.

Though people suffering from back pain may worry that exercise could make the pain worse, it's not likely to as long as you don't overdo it, Albert said.

The diet: Aerobics is more effective when combined with a diet that is low in fat and calories. Reducing caloric intake and increasing active exercise will result in weight reduction. “The diet should include everything like poultry, vegetables, fruits, dairy products etc. but in small proportions. Make sure that the use of sugar and oil is decreased. Intake of ample amount of water and other fluids are also essential in improving the immune system.”

Original Article

The Role of L- Arginine in Lithium Induced Nephrotoxicity in Albino Rats a Morphological Study

1. Ghulam Mujtaba Kolachi 2. Raees Ahmed 3. Santosh Kumar 4. Irum Quddos

1. Asstt. Prof. of Anatomy, Dow Medical College, DUHS, Karachi 2. Asstt. Prof. of Anatomy, Sindh Medical College, DUHS, Karachi 3. Asstt. Prof. of Anatomy, Sindh Medical College, DUHS, Karachi 4. Lecturer of Anatomy, Sindh Medical College, DUHS, Karachi

ABSTRACT

Objective: To observe the protective role of L-Arginine on kidney from toxic effects of Lithium carbonate in Albino rats.

Design: A prospective experimental study.

Place and duration of Study: The study was conducted at Department of Anatomy, Basic Medical Sciences Institute, Jinnah Postgraduate centre Karachi from July 2007 to November 2007.

Materials and Methods: Forty five adult albino rats of either sex were taken and were taken and divided into three groups as A, B and C which were further divided into to three subgroups according to the period of treatment they received i.e. two, four and six weeks respectively. Group 'A' animals served as control and Group 'B' animals received Lithium carbonate (Neurolith, Adamjee Pharma), 20 mg/kg/day with feed. Group 'C' animals received Lithium carbonate 20 mg/kg/day plus L-Arginine (Arginine, General Nutritional Corporation, Pittsburg USA) 300 mg/kg/day with feed. After completion of respective period of treatment, kidneys were removed and fixed in alcoholic formalin and 10% formalin, after processing were embedded in paraffin. 5 μ thick longitudinal sections were cut and stained with PAS-Haematoxylin and Gomori's calcium phosphate method for study of cell morphology.

Results: PAS-Haematoxylin stained sections of group 'A' revealed normal renal cortical histology. Gomori's calcium phosphate method stained tissue revealed normal activity of alkaline phosphates. Group 'B' revealed altered renal histology with damage to the proximal tubules on PAS-Haematoxylin stained sections. Gomori's calcium phosphate method stained sections revealed decreased activity of Alkaline phosphatase in proximal tubules. Group 'C' revealed normal cortical architecture except very mild alteration to brush border in subgroup 'C3'. Gomori's calcium phosphate method stained sections revealed normal activity of Alkaline phosphatase.

Conclusion: The present study suggests that even in therapeutic dose lithium carbonate causes damage to the proximal tubules in albino rats and L-Arginine minimizes the toxic effects of lithium carbonate.

Key Words: Lithium carbonate, PAS-Haematoxylin, Gomori's calcium phosphate proximal tubules, albino rats.

INTRODUCTION

Arginine (symbol Arg or R) is an amino acid. The L form is one of 20 most common natural amino acid. Infants are unable to effectively synthesize L-Arginine making it nutritionally essential for infants¹. Arginine was isolated from a Lupin seedling extract in 1886 by the Swiss Ernest Schulze¹.

The importance of Arginine is attributed to its role as a precursor for nitric oxide that is synthesized in mammalian cells from L-Arginine by nitric oxide synthase². Nitric oxide produces blood vessel relaxation³. Arginine gives rise to nitric oxide by the reaction Arginine to citrulline + nitric oxide, which is catalyzed by nitric oxide synthase⁴. Preliminary evidence suggest that Arginine may be useful in the treatment of medical condition that are improved by vasodilatation, such as angina arthrosclerosis, coronary artery disease, erectile dysfunction, heart failure

intermittent claudication/peripheral vascular disease and vascular headaches³.

The L-Arginine/nitric oxide pathway seems to have slightly protective effect on kidney after ischaemic renal perfusion in rats⁵. Oxidative damage of vascular endothelium represents an important initiation step in development of arthrosclerosis which can be prevented by L-Arginine/nitric oxide pathway⁶.

Nephrotoxic effects of analgesics, antibiotics such as aminoglycosides, anticancer agents such as cisplatin and other chemicals used in industries are known since long time⁷. Lithium therapy has long been associated with nephrogenic diabetes insipidus, chronic interstitial nephritis and minimal change nephropathy⁸. Lithium is now the drug of choice for treating Bipolar affective disorder. It is successful in improving both the manic depressive symptoms in 70-80% of patients. Lithium may also used to treat alcoholism, schizoaffective disorders, and cluster headaches. Thus

lithium is an indispensable pharmaceutical component of modern psychiatric therapy⁹. Proximal renal tubular cells are particularly vulnerable to the toxic actions of chemicals owing to the high energy demands such as reabsorptive and secretory functions⁷. With this background this study was designed to observe the morphologically role of L-Arginine on lithium induced nephrotoxicity in albino rats.

MATERIALS AND METHODS

The present study was conducted in the Department of the Anatomy, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre Karachi. 45 adult Albino rats of either sex between 90 -120 days were selected for present study. Animals were observed for a week for any abnormality before the commencement of this experimental study. The animals were divided in to three groups A, B and C. Each group was further subdivided in to three subgroups according to the period of treatment they received, i.e. 2, 4 and 6 weeks respectively. Each group comprised of five animals.

Group A animals served as control and Group B animals received Lithium carbonate (Neurolith, Adamjee Pharma) at the dose of 20 mg/kg/day with feed and Group 'C' animals received Lithium carbonate 20 mg/kg/day plus L-Arginine (Arginine, General Nutrition Corporation, Pittsburg USA) 300 mg/kg/day with feed.

After completion of their respective period of treatment the animals were anaesthetized with ether in a glass chamber and were fixed on dissecting board and animals were sacrificed and abdomen were opened by midline incision, and kidneys were excised and fixed in alcoholic formalin and 10% formalin for 24 hours. After fixation tissues were processed in higher grades of alcohol from 70-100%, cleared in xylene infiltrated and embedded in paraffin. 5 μ thick longitudinal sections were cut on rotatory microtome. Sections were stained with PAS-Haematoxylin technique and Gomori's calcium phosphate method.

RESULTS

Control Group;

Kidneys appeared oval or bean shaped dark red to dark brown in color, soft in consistency with a smooth and shiny surface, covered by a delicate fibrous capsule which stripped off easily in all the animals of group 'A'. Examination of PAS-Haematoxylin stained sections under light microscope showed proximal tubules closely packed and were circular, oval or elliptical in shape, mostly confined to cortex particularly in vicinity of glomeruli. The lining epithelium of proximal tubules was arranged regularly on intact and well defined basement membrane. The cells appeared low columnar having nuclei located in the centre or basal portion of

the cells. Brush border was found distinct on luminal surface of tubules. There was no nuclear and epithelial debris in the lumen. Gomori's calcium phosphate stained sections showed the site of enzymatic activity of alkaline phosphatase in the proximal tubules in the form of brownish black deposits, which were seen regularly arranged within tubules.

Treated Group:

Group B;

On gross examination of kidney of subgroup B1 appeared reddish brown in color, oval in shape. Their capsules stripped off easily from kidneys. The kidneys of subgroup B2 animals also appeared reddish brown in color, oval in shape but appeared swollen as compared to subgroup A2 and their capsules stripped off with difficulty. The kidneys of subgroup B3 albino rats appeared shrunken in size and light brown in color and their capsules were removed with difficulty.

The microscopic examination of PAS-Haematoxylin stained sections of kidneys subgroup B1 revealed renal architecture with distorted arrangement. The proximal tubules showed epithelial casts in the lumen. The microscopic examination of subgroup B2 and B3 revealed irregular cortical architecture. The proximal tubules were found dilated and filled with cellular debris, sloughed off material and casts. The cells of proximal tubules were found containing nuclei displaced from centre and appeared irregular in size and shape. Epithelial casts and nuclear debris was prominent in the lumen of proximal tubules. Brush border appeared damaged and basement membrane was distorted. There was marked leukocytic infiltration in the interstitium suggestive of inflammatory process. Gomori's calcium phosphate stained sections showed decrease in brownish black deposits in B1, B2 and B3 respectively, suggesting damage to the brush border leading to alterations in pattern of activity of the alkaline phosphates on proximal renal tubular cell.

Group C;

On gross appearance the kidneys of subgroup C1, C2 and C3 which were treated with lithium carbonate and L-Arginine appeared oval or bean shaped dark red in color, soft in consistency with smooth and shiny surfaces covered with delicate capsule which stripped off easily.

Microscopically subgroups C1 and C2 revealed renal architecture with no change in renal tubules and malpighian corpuscles. The lining epithelium of proximal tubules were arranged regularly on intact and well defined basement membrane. Nuclei were present with prominent nucleoli. Brush border was distinct and basement membrane intact. There was no evidence of inflammatory infiltration in the interstitium. The subgroup C3 revealed renal architecture same as compared to the control subgroup A3 apart from brush border was found indistinct and scanty in some tubules.

the Gomori's calcium phosphate stained sections showed distribution of activity of alkaline phosphatase regularly suggestive of intactness of brush border of proximal tubules.

DISCUSSION

L-Arginine is alpha amino acid, in mammals it is classified as semi essential amino acid depending in the stage and health status of the individual¹. Supplementation is some times required³. Infants are some times able to synthesize Arginine making it nutritionally essential amino acid for infants¹. Arginine is involved in numerous pathways of human metabolism. It serves as precursor for the biosynthesis of proteins and also ornithine, polyamines and nitric oxide. Arginine increases GFR and renal plasma flow¹⁷. Nephrotoxicity is an inherent adverse effect of certain anticancer drugs for example streptozocine, cisplatin etc¹². Long term uses of lithium in therapeutic concentrations have been thought to cause histological and functional changes in kidney. The significance of such changes is not clear but is of sufficient concern to discourage long term use of lithium unless it is definitely indicated¹³. In this study the morphological examination of renal cortical tissue in lithium treated subgroup B showed abnormal dilatation of proximal renal tubules. This is in conformation with studies of Christensen S at al., 1982. Vacuolar degeneration was noted in the Group B treated rats this is an adoptive response¹⁴. Over all reduction in volume of cell was observed when compared to the corresponding controls^{15,16}. The histological damage found in lithium treated group was attributed to the biochemical alterations. It is speculated that increased lipid peroxidation as a result of reduced endogenous oxidant capacity may be the initial event in producing renal damage¹⁰. Damage to antioxidant enzymes led cells unprotected from the effects of lithium as super oxide dismutase (SOD), Catalase (CAT) and Glutathion Peroxidase (GSH-Px) were decreased leading to damage to mitochondria and disturbance of ATP production¹⁰. This lead to the damage to tubular cells and the nitric oxide component of L-Arginine appear to have protected group C rats from nephrotoxic effects of lithium carbonate.

CONCLUSION

It is concluded from this experimental study that nephrotoxicity produced by lithium carbonate could be minimized by supplementation of L-Arginine.

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Address for Corresponding Author:

Dr. Ghulam Mujtaba Kolachi,

Assistant Prof. of Anatomy,

Dow Medical College, DUHS, Karachi.

Original Article

Serum and Urinary Inorganic Phosphate in Stone Formers and non Stone Formers at Peshawar

1. Muhammad Ishaq 2. Fakhrul Islam 3. Said Muhammad 4. Mushtaq Ahmad
5. Israr Ahmed Akhund

1. Prof. of Surgery, JMC, Peshawar 2. Asstt. Prof. of Surgery, Bacha Khan MC, Mardan
3. Assoc. Prof. of Medicine, JMC, Peshawar 4. Assoc. Prof. of Ophthalmology, JMC, Peshawar
5. Prof. of Physiology, JMC, Peshawar

ABSTRACT

Background: Geographical variation in the rates of kidney stones has been observed for many years. Pakistan is situated in stone belt. Calculus diseases is endemic in Pakistan, perhaps the incidence in Pakistan is highest in the world.

Objective: To evaluate etiology and biochemical risk factors (inorganic Phosphate) in the Peshawar.

Place and duration of Study: The study was carried out at Leady Reading Hospital, Hayatabad Medical Complex, Peshawar for the period of nine months.

Patients and Methods: Study was conducted at LRH and Hayatabad Hospitals of Peshawar for the period of nine months. Two hundred patients and same number of controls were selected.

Results: The mean value of mean inorganic phosphate in non stone formers were less than that of stone formers. The mean of urinary inorganic phosphate excretion in stone formers was greater than that of non-stone formers.

Conclusion: We conclude that inorganic phosphate is an independent risk factor for renal stone formation.

Key Words: Serum inorganic phosphate, Urinary in organic phosphate, kidney stone.

INTRODUCTION

Urolithiasis or formation of urinary calculi at any level of the urinary tract is a common condition. Urinary calculi are world wide in its distribution but are more common in some geographic areas as in parts of United States, South Africa, Pakistan, India and South East Asia. Geographical variation in rates of kidney stones has been observed for many years^{1, 2}. It is estimated that approximately 2% of the population renal stone disease at sometimes in their life with a male to female ratio of 2:1. The peak incidence is observed in 2nd and 3rd decades of life. Renal Icalculi are characterized clinically by renal colic as they pass down along the ureter and manifest as haematuria³. No single theory of pathogenesis can properly account for human kidney stone, they are too various and their formation is too complex for simple understanding. Using human tissue biopsies, intraoperative imaging and such physiology data from ten different stone forming groups, we have identified at least three pathways that lead to stones. The first pathway is overgrowth on interstitial apatite plaque as seen in idiopathic calcium oxalate stone formers, as well as stone formers. In the second pathway, there are crystal deposits in renal tubules that were seen in all stone forming groups except the idiopathic calcium oxalate stone formers. The third pathway is free solution crystallization⁴. Recent studies have suggested a defect in phosphate balance as a

significant under lying cause of calcium urolithiasis⁵. Present study was planned to examine the relation between inorganic phosphate and upper urinary tract diseases.

PATIENTS AND METHODS

Two hundred patients with upper urinary tract stone disease were selected same number of healthy controls were also added. The study was carried out at Leady Reading Hospital, Hayatabad Medical Complex, Peshawar for the period of nine months. The detailed clinical history and physical examination were carried out, A Performa giving detail of patient's history and family history was filled for each patient. The diagnosis of urinary stone in upper tract was made by X-Ray evidence of stone in renal or ureteric area and history of spontaneous passage of stone in the urine. Microscopic examination of urine was carried out. The patients having serum creatinine of more than 1.3mg.dL were also included in the study. 5cc of blood samples were collected from subjects with aseptic measures during early morning time for estimation of serum creatinine & inorganic phosphate, that were measured by Jaffe's reaction and molybdenum blue method respectively student's "t" tested was done for statistical significance in between various parameters.

Serum Inorganic Phosphate in stone Formers (S.F) and Non-Stone Formers (N.S.F).

The calculated mean levels of serum inorganic phosphate are shown in table. The mean \pm S.D of 100 stone formers and 100 non-stone formers was 5.07 ± 1.22 mg/dl and 4.65 ± 0.39 mg/dl respectively. The mean value in N.S.F is less than that of S.F and the difference is statistically significant ($P < 0.05$).

Urinary Phosphate Excretion:

The mean of urinary inorganic phosphate excretion in S.F (1017 ± 0.915 mg/24 hours) is greater than that of N.S.F (837.02 ± 19.03 mg/24 hours) and statistically it is significant ($P < 0.05$).

Table: Mean \pm S.D serum/urinary inorganic phosphate level in stone formers (S.F) and non-stone formers (N.S.F) at Peshawar and Abbottabad. (n=100).

	Serum		Urinary Excretion	
	S.F	N.S.F	S.F	N.S.F
	mg/dl		mg/24 hours	
Mean \pm S.D	5.07 ± 1.22	$4.65 \pm 0.39^*$	1017 ± 0.915	$837.02 \pm 19.03^*$

* = $P < 0.05$

DISCUSSION

Parathyroid gland regulates the serum concentration of calcium and inorganic phosphate. Their product is always constant. Thus they are inversely related to each other. In our study at Peshawar, it was seen that serum inorganic phosphate as 5.07 ± 1.22 mg /dl and 4.65 ± 0.39 mg /dl in S.F and N.S.F respectively. Shah Jehan and Rehman demonstrated serum inorganic phosphate as 3.83 ± 0.34 and 3.43 ± 0.28 mg/dl in control adults and stone former adults respectively⁶. The difference is statistically not significant. Khanum has demonstrated serum inorganic phosphate as 4.75 ± 0.22 and 5.11 ± 0.13 mg/dl in controls and stone formers respectively⁷. The difference is being statistically not significant. Hussain showed serum inorganic phosphate as 3.99 ± 0.39 , 3.81 ± 0.69 and 3.57 ± 0.96 mg/ dl in controls, sign episode S.F and recurrent S.F⁸. The difference between the three groups are being statistically not significant. If we compare the serum levels of inorganic phosphate of these four studies it is evident that our study at Peshawar showed statistically significant difference regarding inorganic phosphate which acts as a definitive risk factor in the upper urinary tract stone disease. Khanum reported daily excretion of inorganic phosphate as 268.61 ± 16.00 and 272.88 ± 1.89 mg/ day respectively in stone former and non – stone former. While Shah Jehan and Rehman, reported urinary excretion of inorganic phosphate 530.0 ± 0.05 mg/day and 630 ± 0.06 mg /day in S.F and N.S.F respectively⁶. Hussain et al, reported a urinary excretion of inorganic

phosphate 26.3 ± 6.59 , 30.22 ± 8.74 and 28.37 ± 9.82 in N.S.F, S.F and control. He showed that this difference is not statistically significant⁸. In comparison of these studies with our study urinary excretion of inorganic phosphate is 1017 ± 0.915 and 837.02 ± 19.03 in S.F and N.S.F. In our study it was statistically significant. The difference may be due to the fact that increased meat consumption in Peshawar may produces hyperphosphaturia, the effect of increased parathyroid hormone and those having a positive family history are at increase risk of upper urinary tract stone disease.

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Address for Corresponding Author:

Muhammad Ishaq,
Professor of Surgery,
Jinnah Medical College,
Peshawar.

Original Article

Survival Probability of Plasmodium Falciparum against Chloroquine and its Combination with Sulphadoxine-Pyremethamine in Punjab, Pakistan

1. M. Saleem Rana 2. Akhtar Tanveer 3. Asma Abdul Latif 4. Ammara Hassan Tahir

1. Assoc. Prof., Health Services Academy, Islamabad 2. Prof. of Parasitology, Punjab University, Lahore
3. Asstt. Prof. of Zoology, Women College University, Lahore 4. Asstt. Prof. of Medicine, AIMC, Lahore

ABSTRACT

Purpose of study: Survival probability of *P.falciparum* was determined against the chloroquine and its combination with sulphadoxine-pyremethamine.

Type of study: Prospective nonrandomized descriptive study.

Place and duration of study: Study was conducted in five districts “Muzaffargarh, D.G.Khan, Jhang, Sheikhpura and Multan” of Punjab, Pakistan. During the non-transmission season of the year 1999 to 2000 and 2008, among the rural populations 5952 persons were screened for malarial parasites.

Methodology: During the malaria non transmission season (November, December & January), 5952 persons were screened for malaria and 1409 positive cases were detected. 404 subjects out of total positive cases were selected to be tested against chloroquine and 50 with combination of chloroquine and sulphadoxine-pyremethamine by in vivo technique. Follow up was carried out for 28 days (on day 1, 2, 3, 7, 14, 21 and 28).

Result: Over all 35.4 % resistance-I was detected against chloroquine monotherapy and 4% with combination therapy (chloroquine and sulphadoxine-pyremethamine). Resistance-III was not found. Two variables were found important predictors of drug resistance; a young child and a high parasitaemia count ($>6000/\mu\text{l}$) at day 0.

Conclusion: It is concluded that malaria is still significant problem and resistance against monotherapy is increasing, hence adoption of combination therapy as first line treatment for uncomplicated falciparum malaria in Punjab Pakistan is recommended.

Key Words: Plasmodium falciparum, resistance, chloroquine, Pakistan

INTRODUCTION

The efficacy of readily affordable antimalarial drugs is declining rapidly in different parts of the world (1, 2). Drug resistance (%) was found significantly less 5.3 (4/77) in combination of artesunate and sulphadoxine-pyrimethamine, than monotherapy of chloroquine 71.8 (51/71) or sulphadoxine-pyrimethamine 44.1 (3). Later continuous studies were conducted in Pakistan as per results given in Figure-1. Keeping in view the fluctuated trend in the malaria drug resistance in Punjab the present study was planned and conducted.

MATERIALS AND METHODS

This study was carried out on 404 subjects of uncomplicated *falciparum* malaria with monotherapy of chloroquine and on 50 subjects of uncomplicated *falciparum* malaria with combination therapy of chloroquine and sulphadoxine-pyrimethamine. The study subjects were selected from the both sexes, all age groups except < 6 months babies, with the history of fever $\geq 38^{\circ}\text{C}$, from any occupation. The area of the

study was selected on the basis of malaria endemicity in the province of Punjab, Pakistan by record review. To select the subjects for studies important characteristics (4) were parasite density minimum threshold of $1000/\mu\text{l}$ (asexual parasites per micro-liter) and maximum threshold of $80,000 / \mu\text{l}$ of blood, positive for *P.falciparum* mono-infection, any subject had not received any antimalarial drugs during previous four weeks. For detection of antimalarial drugs urine test of the patients was conducted and positive subject were excluded. The studies were carried out during the winter season (After 15th November to before 15th January) the non-transmission season in Pakistan to minimize the chances of new infection (5). Test drugs were administered by weight of the subject as per treatment policy. Follow-up blood slides were obtained on day 1, 3, 7, 14, 21 & 28 for monitoring the course of asexual parasitaemia. Written or oral consent, as appropriate was obtained from all subjects from whom blood samples were taken. Thick and thin film was prepared by obtaining finger prick blood, stained for 30

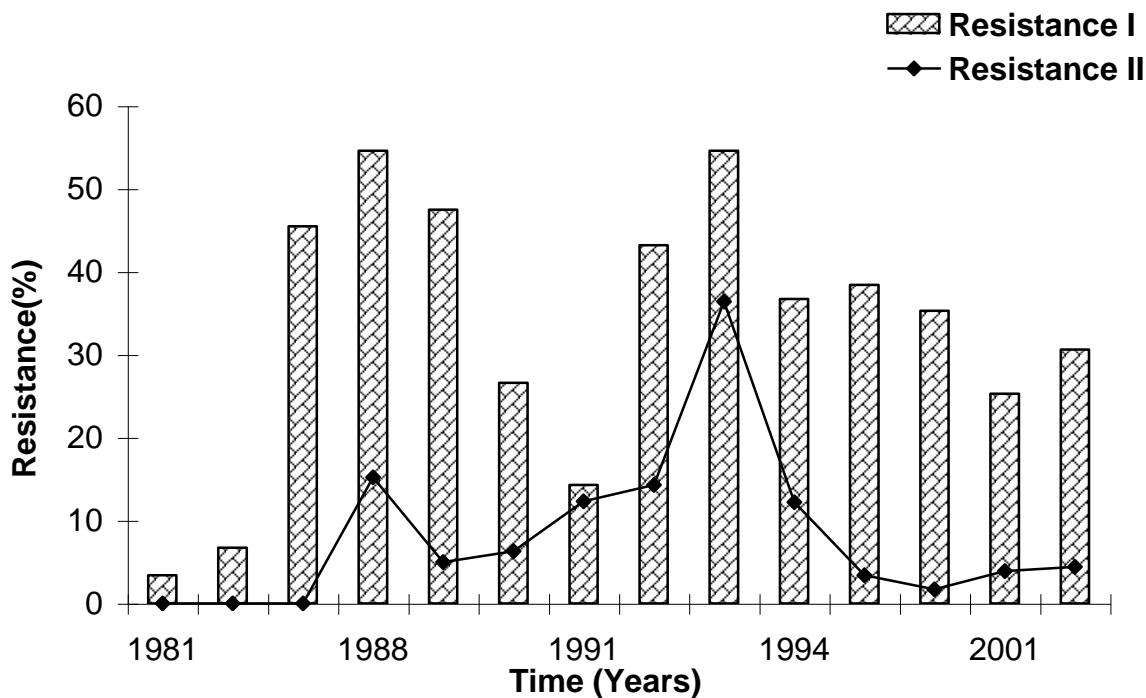


Figure-1: Showing the resistance against chloroquine from 1981 to 2004(Curtsy of Directorate General Health Punjab, Pakistan, 2008).

minutes with Giemsa 1 % (v/v) in the water of pH 7.2 and examine under oil immersion. Subjects for study were not enrolled with the history of pregnancy and lactation or sever malaria cases (cerebral, renal malaria). One or more of the general danger signs or any other sign of severe and complicated malaria, presence of any severe disease, presence of severe malnutrition, febrile diseases other than malaria. Survival probability of *P.falciparum* against chloroquine and its combination with sulphadoxine-pyrimethamine was determined and analyzed by using the Kaplan-Meier method. Early and late failures were distinguish by dividing the follow-up in 28-days. Differences in proportions were analyzed by using chi-square (6).

RESULTS

Chloroquine efficacy was assessed on 404 subjects of uncomplicated *falciparum* malaria and found 35.4 % (143/404) resistance ($p < 0.001$). As high parasite density is predictor of fatality, similarly high density predicts the resistance development against *P.falciparum* in various areas.

For all subjects, observations were recorded for 28 days or till treatment failure or loss of follow-up, if either occurred in the mid of study, this information were recorded as drug resistance. Parasite density/ μ l of resistant subjects and sensitive subjects was also found important factor toward causing the resistance. In

resistant subjects 53.84% (77/143) had parasite density >6000 parasite/ μ l, 28.677% (41/143) had 3000 to 6000 and 17.48% (25/143) had density <3000 parasite/ μ l, statistically difference was found highly significant (Figure-2). Survival of subjects was estimated by using the Kaplan-Meier method (Figure-3) and found 100 % on day one. Survival (%) of subjects reached at zero with parasite density 28000 / μ l on day one having RII level of resistance. Subject having parasite density 30000/ μ l with RI resistance found zero percent survival.

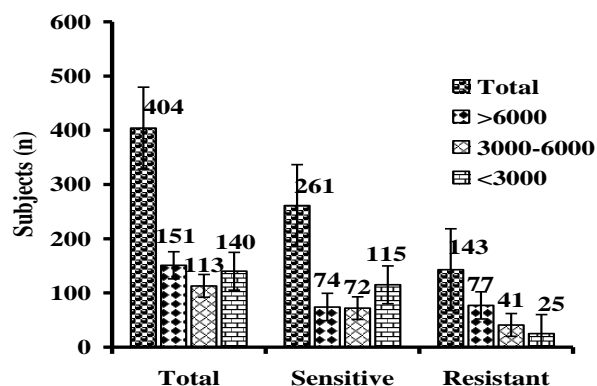


Figure-2: Showing the total, sensitive and resistant subjects of chloroquine against *Plasmodium falciparum* in different groups of subjects having different parasite density / μ l by *in vivo* technique in five districts of Punjab, Pakistan from 2003 to 2005.

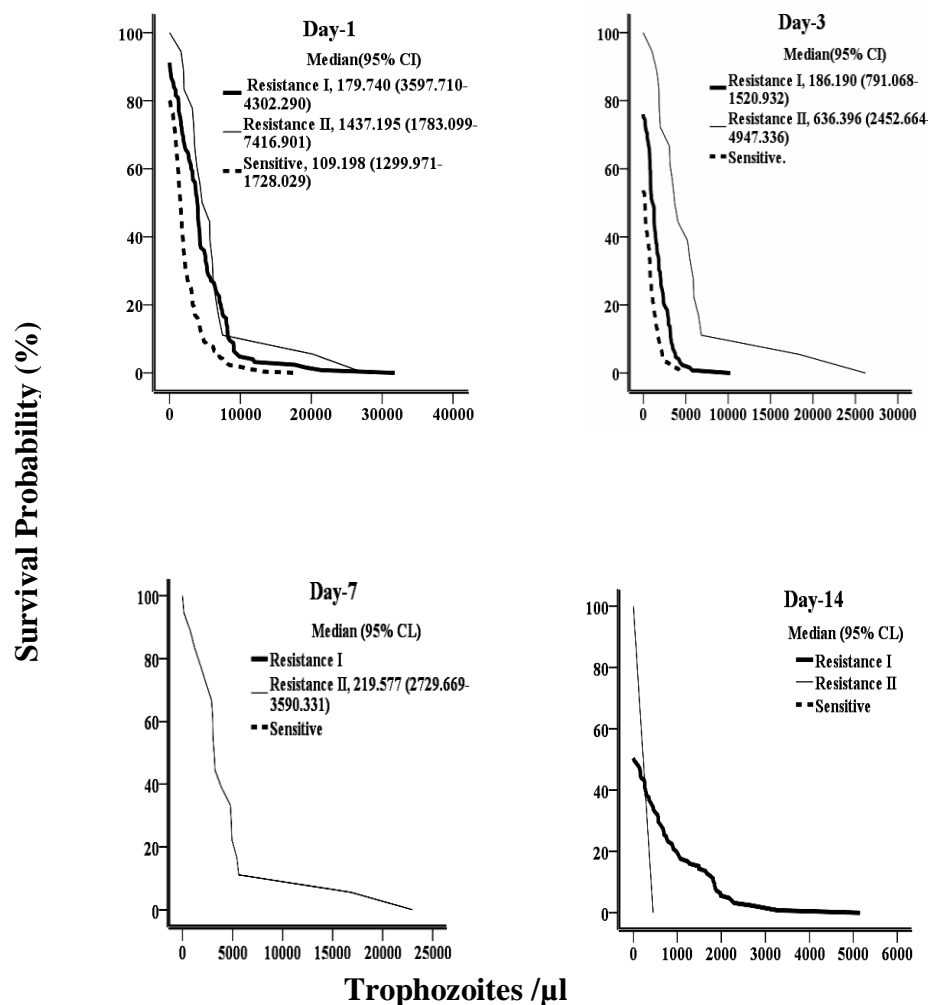


Figure-3: Showing the survival of subjects on every follow-up day (1, 3, 7 and 14) with different parasite density/ μ l by Kaplan Meier for all subjects studied by *in vivo* technique in five districts of Punjab, Pakistan from 2003 to 2005.

Subject having parasite density 15000 / μ l had survival (%) 10 with resistant strains. On day three survival (%) was found 100 with zero parasite density/ μ l, which decreased with the increase of parasite density/ μ l and reached zero percent survival with parasite density 3000/ μ l for sensitive and subjects having parasite density 4000/ μ l resistance strains (Figure-4).

On day three survival (%) was found 100 with zero parasite density/ μ l, which decreased with the increase of parasite density/ μ l and reached zero percent survival with parasite density 28000/ μ l for RII and subjects having parasite density 10000/ μ l with RI resistance

found zero percent survival. Same pattern was found on all follow-up days.

DISCUSSION

In this trail mono and combination therapeutic effects were tested against *P.falciparum* on chloroquine and combination of chloroquine/sulphadoxine-pyrimethamine in Punjab, Pakistan. Chloroquine was known as the most effective and safe antimalarial (7) but the development of resistance to chloroquine against *P.falciparum* has become a serious problem for malaria treatment (8).

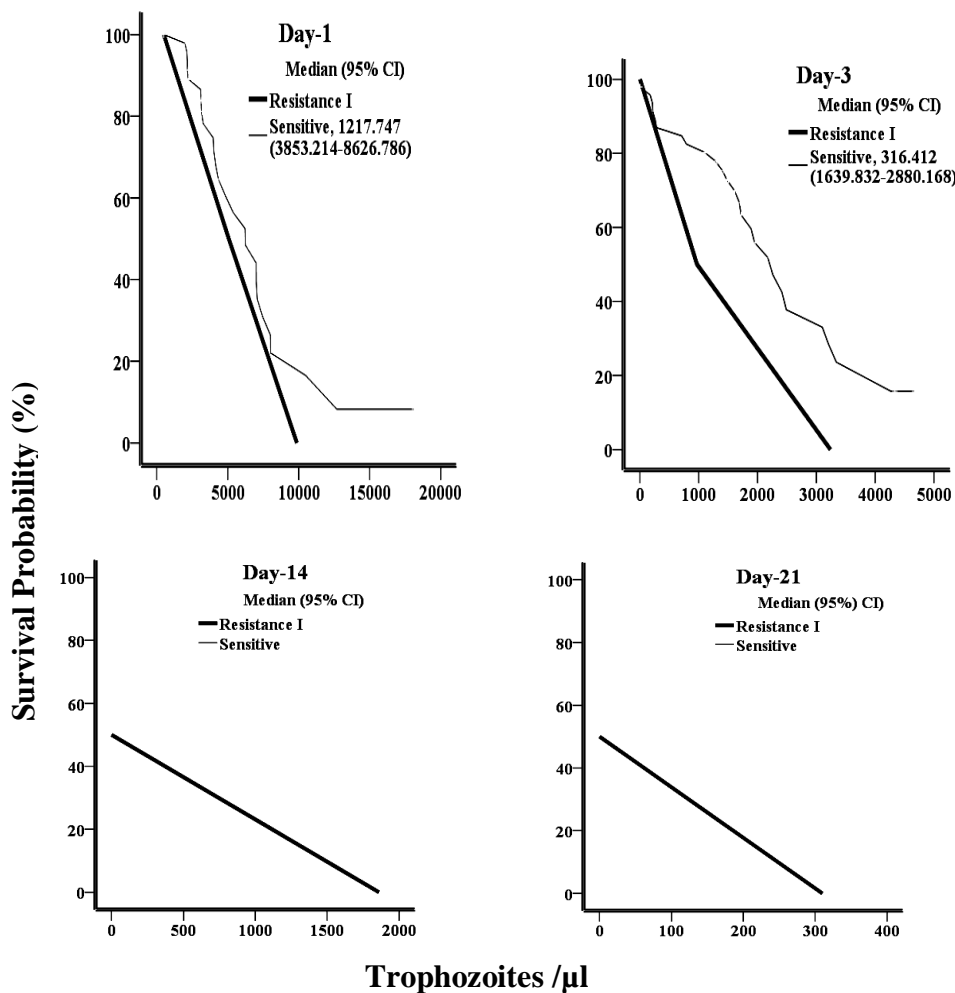


Figure-4: Showing the survival of parasite on every follow-up day by Kaplan Meier for all subjects studied by *in vivo* technique in one district of Punjab, Pakistan on combination therapy against *Plasmodium falciparum*. Study subjects were analyzed on day1, 3, 14 and 21. $P < .000$ [95% CI = .000-.000].

In present study SPR noted was 27.4% which is 31.6%, 18% and 40.3% less than reported SPR by 15, 18 and 19 as they reported 59%, 45.4 and 67.7% respectively. This showed that in Punjab, Pakistan still SPR is less than other malarious countries in the world.

The resistance reported in the present study was 35.4% in the same rang (30.6 to 39) as reported by (9). Reported resistance (%) by (10) was less than present study, the reason of low resistance (%) would be the very initial stage of resistance emergence in Punjab, Pakistan in 1985. Globally resistance (%) to chloroquine against *P.falciparum* has been also reported by many authors (11) noted resistance (%) 47.9, 28, 23.1, 16.9, 42.5, 29.4 and 12.8 more respectively than present study. This showed that the development of resistance exists almost in the all malarious countries of the world.

In present and other studies conducted by different researcher in Punjab, Pakistan resistance of grade III

was not noted, except one case from district Rahim Yar Khan by (12) in a traveler came from Saudi Arabia. District wise analysis of present study data showed 41.6, 50, 41.6, 44.5, 25, 27.8 and 36.2% resistance in Sheikhupura, Muzaffargarh, Multan, Jhang, Faisalabad, Lahore and D.G.Khan respectively. The reason may be the topographical difference of areas. In 1984 resistance (%) was recorded 20 in district Multan (13), which have been increased 21.6 as per report of present study. The apparent reason of increase in district Multan is high *falciparum* malaria (31.6%) as compared to other study districts. 54.5 resistances (%) to chloroquine were reported in Faisalabad by (14), now it was detected 25%. In Faisalabad resistance (%) decreased, might be due to low FPR (16.8%). Resistance (%) in district Muzaffargarh was noted 44.4 in 1987, 46.6 in 1996, 31.2 in 1997 and 50 in present study. District Muzaffargarh is one of the districts where resistance (range 31.2-50) has been reported since 1987. In

Sheikhupura resistance was found 33.3% (15) and 41.6 during present study which showed increased trend.

Parasite density/ μ l was found very significant factor as it is directly proportional to the resistance (%). 53.8% resistance was noted among the subjects having ≥ 6000 parasite density/ μ l. Similarly (16) had reported that high parasitaemia count was one of the important and independent predictors of resistance emergence and spread. This finding offered us unique opportunity to look at predictors of resistance. Our definition of time to develop resistance was based on the parasite's ability to grow despite the presence of chloroquine in the blood and the role of patient's immunity. A similar findings were noted by the (16, 17). In this study, we have examined the efficacy of the combination of chloroquine and sulphadoxine-pyrimethamine for treating uncomplicated falciparum malaria in Punjab Pakistan, compared to either with chloroquine or sulphadoxine-pyrimethamine alone. The resistance (%) of chloroquine monotherapy over 28 days was 35.4% in this study thus chloroquine is no longer useful as first-line treatment for malaria in Punjab Pakistan (18), suggested change of drug if resistance development increases more than 10% in order to prevent deaths. Change of drug is suggested on 25% resistance (19). The combination of chloroquine/ sulphadoxine-pyrimethamine is an efficacious treatment for uncomplicated malaria in Punjab Pakistan as resistance (%) was detected 4 (2 of 50) in the present study. The efficacy of chloroquine/sulphadoxine-pyrimethamine in Gambia had reported 13.9% in 2006 (20). The use of basoquine and sulphadoxine-pyrimethamine in combination is highly effective (21).

These preliminary results demonstrate the need for carefully designed studies to measure the contribution of resistant parasites to inadequate treatment of uncomplicated malaria in Punjab as combination treatments become more widely deployed. The drug resistance of same combination (Sulphadoxine-pyrimethamine and chloroquine) against uncomplicated P.falciparum also checked and reported 98.2%, 92.7% and 97% effectiveness respectively (22). This indicated that combination of sulphadoxine-pyrimethamine with chloroquine is effective remedy for treatment of resistant P.falciparum cases. The ACT ("artemisinin based combination therapy" artemisinin with sulphadoxine-pyrimethamine or artemisinin with 4-aminoquinoline) is a potential drug for the treatment of falciparum malaria.

Monotherapy of chloroquine, basoquine and sulphadoxine-pyrimethamine for treatment of falciparum malaria should be stopped. Artemisinin based combination therapy (ACT) should be adapted, as the combination of a short acting drug like artemisinin with a long acting drug like sulphadoxine-pyrimethamine has the advantage that any parasites

remaining after the artemisinin derivative has taken effect are eliminated by a drug with a different mode of action. Rapid test for diagnosis of malaria is recommended for early detection and prompt treatment to achieve the millennium development goal (MDGs). 28-day follow-up test technique is recommended for in vivo resistance studies because it is not possible to detect RI by adopting 7-day or 14-day test technique. It is necessary to first map up the distribution and frequency of resistance through out the country. The use of molecular approaches to enhance the understanding of effective interventions will be useful.

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Kampala, Uganda. *Am J Trop Med Hyg* 2003; 68(2): 127-32.

Address for Corresponding Author:

Muhammad Saleem Rana,
Associate Professor,
Health Services Academy,
Islamabad.

Original Article

Evaluation of Histopathological and Biochemical Hepatoprotective Potentials of *Fagonia Bruguieri* A Plant from Cholistan Desert

1. Khalid Usman 2. Shahid Habib 3. Rao Arif

1. Assoc. Prof. of Pathology, QAMC, Bahawalpur 2. Assoc. Prof. of Pathology NMC, Multan

3. Asstt. Prof. of Physiology, NMC, Multan,

ABSTRACT

Objective: Aerial parts of *Fagonia Bruguieri* (FB) (family, zygophyllaceae) were subjected to in vivo hepatoprotective study in order to validate its traditional use in hepatobiliary disorders, by native people of Cholistan desert, Pakistan.

Design of Study: Experimental study.

Place of study: This study was conducted at PCR lab Multan.

Materials & Methods: The animals were randomly divided into three groups, containing 10 rabbits in each group. Hepatoprotective effects of pre-treatment with aerial parts (ethanolic extract) of FB (500 and 750 mg/kg/day PO for 7 days) against CCl₄ (0.75 ml/kg, S/C) intoxicated rabbits were evaluated by serum biochemical parameters and liver histological observations. Silymarin (100 mg/kg/day PO for 7 days) was used as a standard hepatoprotective drug,

Results: CCl₄ intoxicated group had raised levels of SGOT, SGPT and ALP significantly but TB level was not raised as compared to normal control group. FB extract (both doses of 500 and 750 mg/kg) showed hepatoprotection as obvious by significant reinstatement of levels of SGOT, SGPT and ALP while TB level was not changed significantly, when compared with CCl₄ intoxicated group. Both doses of FB extract were well comparable with silymarin. Histopathological examination of the liver tissue further corroborated these results.

Conclusion: Therefore, the conclusion of the present study supports the traditional believes on hepatoprotective effects of *Fagonia Bruguieri* (aerial parts).

Key words: *Fagonia Bruguieri*, Hepatoprotection, Carbon.

INTRODUCTION

Cholistan desert is present on the eastern side of Punjab Province (Pakistan)¹. The majority of plants grow in desert have therapeutic properties and native people utilize these plants to treat various diseases².

Fagonia Bruguieri (family; zygophyllaceae) is one of those plants. it is an herbaceous plant and commonly known as "dhaman.dramaho". In folk medicine, powder of the whole plant is used to spread on skin eruptions and boils. Bath of plant boiled in water is very useful in allergies and many other skin diseases³. Its decoction is also recommended in biliousness and hepatomegaly⁴. In case of skin eruptions, whole plant decoction is also recommended³.

Native people of cholistan desert use this plant in hepatobiliary disorders.

Literature survey reveals that a very little work had been carried out on pharmacological activities of this plant. However, to the best of our knowledge, no previous work has been published on hepatoprotective competence of this plant.

The present study was aimed to evaluate the hepatoprotective activity of FB against CCl₄ induced hepatotoxicity.

MATERIALS AND METHODS

Ethanol, CCl₄, formalin, diagnostic kits (SGPT, SGOT, ALP and TB), xylene paraffin wax, eosin, hematoxylin and Canada balsam. The subsequent chemicals were purchased from Merck, Darmstadt, Germany. Silymarin and pentothal sodium was obtained from Abbott Laboratories, Pakistan. Olive oil was from P. Sassp, Italy. All chemicals of analytical grade were used.

Severn rabbits per each group were selected for histological examination. Histological changes were graded as given below⁵.

- Group-0 (Normal): Normal liver morphology; hepatocytes with round nucleus centrally with homogenous cytoplasm, flat endothelial cells around central vein and sinusoid.

- Grade-+1 (mild degree): 1-2 hepatocyte rows around central vein showed; hepatic cell degeneration along

with necrosis (loss of nucleus), less injury of endothelial cells around central vein, less fat vacuoles in hepatocytes.

- Grade +2 (moderate degree): Some hepatocyte rows around central veins showed; swelling, intracytoplasmic vascular degeneration in centrilobular, midzonal and periportal areas endothelial cells around central vein more damage than level +1 more fat vacuoles in hepatocytes than level +1.

- Grade +3 (Severe degree):- 3-4 hepatocyte rows around central vein demonstrated; hepatocytic degeneration and necrosis, degeneration cells including centrilobular, midzonal and periportal areas (Diffuse intra-cytoplasmic vascular degeneration), endothelial

lining aof central vein showed more cell damage, increased fat vacuoles in hepatocytes than level +2, marked focal necrosis.

RESULTS

Administration of CCl₄ (0.75 ml/kg, p.o.) produced a significant increase in serum enzyme levels, namely SGOT, SGPT and ALP. However, TB level was remained unchanged when compared with normal control. The postoperative action of FB aerial parts extracts on CCl₄ induced hepatotoxicity are summarized in table-1.

Table-1

Effects of ethanolic extract of FB (aerial parts) on rabbits serum biochemical parameters after CCl₄ administration

Group	SGOT (iu/l)	SGPT (iu/l)	ALT (iu/l)	TB (mg/dl)	Liver damage (histological scores)
Normal control	40.69 ± 19.94	41.66 ± 23.35	264.5 ± 49.72	0.83 ± 0.22	0
CCl ₄ control	455.2 ± 37.12*	434.2 ± 34.30*	394.3 ± 29.56*	1.32 ± 0.20	+3
Silymarin control	176.5 ± 56.77*°	205.9 ± 36.59*°	257.0 ± 41.00°	1.01 ± 0.42	+1
Test group-1	124.2 ± 51.94°	265.7 ± 52.43*°	273.3 ± 30.82°	1.28 ± 0.25	+1
Test group-2	223.0 ± 58.90*°	278.0 ± 54.09*°	216.7 ± 45.31*°	1.78 ± 0.19*	+1

Values are represented as mean ± SEM (n=10).

0 = Normal

+1= Mild

+2= Moderate

+3= Severe

* P 0.05 compared with normal control group

° P0.05 compared with CCl₄ control group

DISCUSSION

Histological changes after 24 hours of CCl₄ induced liver injury included hepatocytes necrosis, inflammatory cell infiltration, fatty degeneration, hydropic degeneration, vacuole generation and microvascular steatosis. Administration of silymarin (100 mg/kg) and FB extract (both doses at 500 and 750 mg/kg) significantly preserved the almost normal hepatocellular architecture from damaging effects of CCl₄.

CCl₄ induced acute hepatocellular damage is frequently used indicator to date for the assessment of hepatoprotective potential of drugs or medicinal flora and their extracts, both via in vivo and in vitro techniques⁵.

According to phytochemical analysis, FB contains chiefly flavonol O-glycosides, predominantly kaempferol, quercetin, isorhamnetin, herbacetin, triterpenoid saponins, coumarins, many alkaloids and diterpenoids⁶. The flavonoids are well reputed for their antioxidant, free radical scavengers and anti-

lipoperoxidant actions⁷. Similarly, coumarins are also well documented for their antioxidant and hepatoprotective actions⁸. Saponins inhibit lipid peroxidation by scavenging reactive oxygen species⁹. Moreover, alkaloids¹⁰ and triterpenoids¹¹ also have hepatoprotective activity. Flavonoids and quercetin are very fine scavengers and also showed CCB activity and may possibly also have contributed toward hepatoprotective action¹². So it is reasonable to think for a possible relation between the proposed hepatoprotective activity and CCB activity of FB ethanolic extract, due to the presence of these polyphenolic compounds among other plant constituents.

It is reported that the mice knocked out of CYP2E1 gene show resistance against CCl₄ induced hepatotoxicity and the level of reactive metabolites can be reduced by inhibition of CYP2E1 gene expression, consequently tissue injury is reduced¹³. In recent years, there has been an active search for the development of CYP₄₅₀ inhibitors from natural products that may have therapeutic potential in prevention of liver damage.

Triterpene acids, oleanolic acid and ursolic acid inhibit CYP₄₅₀¹⁴. So, the hepatoprotective action of FB extract may be due to the presence of some of the above mentioned compounds which cause down regulation of CYP2E1 gene expression but it must be confirmed after a detail phyto-chemical analysis of the plant.

To be brief, the possible hepatoprotective mechanism of FB aerial parts ethanolic extract of CCl₄ induced liver injuries may be through one of actions prevention of process of lipid oxidation, free radical scavengers or down regulation of CYP2E1 gene expression.

CONCLUSION

It is concluded from the study provides scientific root for the conventional use of *Fagonia bruguieri* in hepatobiliary diseases in Eastern system of medicine, Further studies should be carried out to determine the therapeutic index and exact mechanism of hepatoprotection offered by the plant.

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Address for Corresponding Author:

Khalid Usman,

Associate Professor of Pathology,
QAMC, Peshawar.

Original Article

The Effects of Co2 Pneumoperitoneum on End Tidal CO₂ (ETCO₂), Arterial Blood Pressure and Heart Rate During Laparoscopic Cholecystectomy Under General Anaesthesia

1. Noor Hussain 2. Dure Shahwar 3. Basharat Ali Khan 4. Rehan Masood

1. Prof. of Anesthesia, FUMC, Rawalpindi 2. Assoc. Prof. of Surgery, FUMC, Rawalpindi 3. Assoc. Prof. of Surgery, FUMC, Rawalpindi 4. Asstt. Prof. of Surgery, FUMC, Rawalpindi

ABSTRACT

Objective: To analyze the effects of CO₂ pneumoperitoneum at 13 to 15 mmHg intra-abdominal pressure on end tidal CO₂ (ETCO₂), arterial blood pressure and heart rate during laparoscopic cholecystectomy under general anaesthesia with controlled mechanical ventilation.

Design: Prospective Descriptive Study.

Place and Duration of Study: The study was conducted at the department of anaesthesia Fauji Foundation Hospital Rawalpindi from August 2005 to September 2006.

Patients and Methods: Fifty consecutive ASA grade-1 patients, 47 females, 3 males and aged 35-65 years undergoing laparoscopic cholecystectomy were included in the study. All patients received a standardized balanced anaesthetic in which 0.7 - 1 % isoflurane was used during maintenance. Ventilation was controlled and minute volume was kept at 100 ml/kg/min. Pneumoperitoneum was created with CO₂ at a flow rate of 10 liter/min and 13 to 15 mmHg intra abdominal pressure was maintained during the operation. End tidal CO₂ (ETCO₂), heart rate and non invasive systolic, diastolic and mean arterial blood pressure was recorded immediately before intra abdominal CO₂ insufflation and then after 5 minutes interval during the period of CO₂ pneumoperitoneum. Study period started immediately before intra-abdominal CO₂ insufflation till about 60 minutes of surgical procedure.

Results: The end tidal CO₂ (ETCO₂) levels progressively increased to reach a plateau 36mmHg 20 minutes after the beginning of intra abdominal CO₂ insufflation. The end tidal CO₂ (ETCO₂) levels increased to 21 % of base line (from 30 to 36 mmHg) during CO₂ pneumoperitoneum for laparoscopic cholecystectomy under controlled mechanical ventilation at minute volume 100 ml/kg/min. The systolic, diastolic and mean arterial blood pressure increased to 12% to 17% of the baseline during CO₂ pneumoperitoneum at 13-15 mmHg intra abdominal pressure. There was no significant change in heart rate.

Conclusion: CO₂ pneumoperitoneum produces rise in end tidal CO₂ (ETCO₂) levels and hemodynamic alterations proportional to the increased intra abdominal pressure during laparoscopic surgery under general anaesthesia with controlled mechanical ventilation.

Key Words: General anaesthesia, laparoscopic cholecystectomy, CO₂ Insufflation, Pneumoperitoneum, end tidal CO₂, Blood Pressure, Heart Rate.

INTRODUCTION

Laparoscopic cholecystectomy requires abdominal insufflation with CO₂ and an increase in the intra abdominal pressure to 15 mmHg (1). The physiologic affects of pneumoperitoneum include systemic absorption of CO₂, haemodynamic and physiological alteration in a variety of organs due to increased intra abdominal pressure. CO₂ absorption across the peritoneal surface and into systemic circulation can result in hypercarbia and eventual systemic acidosis. Hypercarbia and acidosis can cause hemodynamic changes by direct action on the cardio vascular system and by an indirect action through sympathoadrenal stimulation (2, 3). To prevent hypercapnia, close intra

operative monitoring of end tidal CO₂ (ETCO₂) or arterial partial pressure of CO₂ (PaCO₂) is therefore essential. ETCO₂ level is an easily accessible monitoring parameter than PaCO₂. The increased intra abdominal pressure during pneumoperitoneum has been shown to result in hemodynamic alteration and changes in femoral venous flow, renal, hepatic and cardio pulmonary function (4, 5). Longer the operative time during laparoscopic surgery, longer will be the exposure of the host to the adverse physiologic effects of pneumoperitoneum. Appropriate anaesthetic techniques and monitoring facilitate surgery and allow early detection and reduction of complications.

The purpose of study is to determine the effects of CO₂ pneumoperitoneum at 13 to 15 mmHg intra-abdominal pressure on end tidal CO₂ (ETCO₂), arterial blood pressure and heart rate during laparoscopic cholecystectomy under general anaesthesia with controlled mechanical ventilation.

PATIENTS AND METHODS

Fifty consecutive patients (47 females and 3 males) of ASA Grade -1 with an age range of 35 to 65 years and weighing between 50-80 Kg, undergoing cholecystectomy were included in the study (table-1) . Patients older than 65 years, those with morbid obesity and ASA grade II and above were excluded from the study.

All patients were premedicated with diazepam 10mg orally before midnight and were kept NPO after midnight. Intravenous line was established with 18 gauge cannula on the dorsum of hand. 3mg midazolam was given IV 5mins before induction of anaesthesia. Induction of anaesthesia was with intravenous 0.1mg/kg nalbuphine and thiopentone sodium 5mg/kg. Tracheal intubation was facilitated by IV atracurium 0.5mg/kg. Anaesthesia was maintained with 50% nitrous oxide in oxygen, 0.7 – 1 % isoflurane and intermittent bolus of Atracurium as required. Blease anaesthesia machine and Blease 6500 anaesthesia ventilator with close circuit was used. The ventilatory system was set to maintain a minute volume of 100ml/kg/min, an inspiratory to expiratory ratio of 1:2 and ventilatory frequency of 14 bpm. Monitoring included pulse rate, continuous ECG, intermittent NIBP, pulse oximetry(SPO₂) and capnography (ETCO₂). The cardiac monitor Welch Allyn was used for measuring these parameters.

Patients were placed in a supine position on operating table. Open pneumoperitoneum was created with carbon dioxide at a flow rate of 10 liters per minute and 13 to 15 mmHg intra-abdominal pressure was maintained. Reverse trendelenburg 15 to 20 degrees tilt was made in the beginning of laparoscopic procedure. The average duration of surgery was about one hour.

One liter of Ringer's lactate was given intravenously during the operation. At the end of surgery the neuromuscular blocking agent was antagonized with a combination of Neostigmine 0.05 mg/kg and Atropine 0.02 mg/kg, patients were transferred to the post operative ward and discharged on second post operative day.

Collection of Data

Cardiac monitor was set to record ETCO₂, SPO₂, heart rate and non invasive systolic, diastolic and mean arterial blood pressure immediately before intra abdominal carbon dioxide insufflation and then after every 5 minutes interval during the period of CO₂ pneumoperitoneum in all patients during surgery. The data collection started 10- 20 minutes after induction of anaesthesia, just before intra-abdominal CO₂ insufflations. The record of blood pressure, heart rate

and end tidal CO₂ before induction, after induction of anaesthesia for 15 minutes and during recovery period was not included in the study. The print of the recorded data was taken from the cardiac monitor at the end of each operation.

Statistical Analysis

Data was analyzed using SPSS version 10.0. Mean, standard deviation, standard error of mean (SEM) and percentages were calculated. The statistical analysis was done by students' t-test and p-value less then 0.05 was considered significant.

Table 1: Patients Characteristics (n=50)

Total no. of patients	50
Age (years) mean \pm SD	49 \pm 7.9
Female/ male ratio	47/3 / 94:6
Weight (kg) mean \pm SD	67 \pm 7.5
American Society of Anaesthesiologist 's physical status (ASA grade)	ASA Grade I

RESULTS

Effect on End Tidal CO₂ (PETCO₂)

The PETCO₂ levels increased to 10 % (33 mmHg), 17% (35 mmHg) and 21% (36 mmHg) respectively by baseline (30 mmHg) after 5 mins, 10 mins, and 20 mins beginning of intra abdominal CO₂ insufflation. (Table 2, Fig 1).

The PETCO₂ levels progressively increased to reach a plateau 36 mmHg 20 mins after the beginning of intraperitoneal CO₂ insufflation. The PETCO₂ levels remained 21% elevated during the period of peritoneal insufflation. This 21% increase in PETCO₂ levels from 30 mmHg at base line to 36 mmHg were observed during CO₂ pneumoperitoneum under controlled mechanical ventilation, at a constant minute ventilation 100ml/kg/min and 13-15 mmHg fixed intra abdominal pressure.

The 21% (36 mmHg) increase in PETCO₂ levels by base line (30 mmHg) were statistically significant (P< 0.05)

Effect on Arterial BP and Heart Rate

he systolic, diastolic and mean arterial blood pressure increased to 13 – 14% (132 mmHg systolic, 88 mmHg diastolic, 102 mmHg mean) after 10 minutes, and after 20 to 30 minutes 16 -17% by baseline after beginning of intra abdominal CO₂ insufflation. After 40 minutes systolic, diastolic and mean arterial BP remained 10 – 12% elevated by base line (117 mmHg systolic, 77 mmHg diastolic, 90mmHg mean) during laparoscopic surgery (Table 3, Fig 2).This increase in arterial BP was statistically significant (P < 0.05)

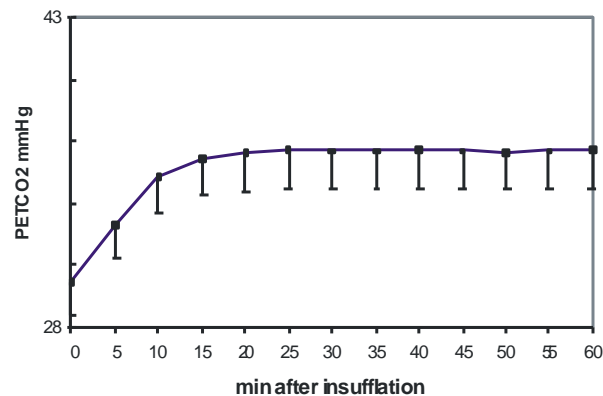
The heart rate slightly increased from 86 beats per minute to 90 beats per minute (Table 4). No significant increase in heart rate was detected during CO₂ pneumoperitoneum for laparoscopic cholecystectomy.

Table 2: Changes in PETCO₂ during CO₂ Pneumoperitoneum for laparoscopic Cholecystectomy (n=50)

	Time	Petco ₂ level MmHg	% >	P-Value
Before beginning of intra-abdominal CO ₂ insufflation	0 min	30.13 ± 0.87		
After beginning of intra-abdominal CO ₂ insufflation	5 min	33.00 ± 0.95	9.51%	P<.05
	10 min	35.30 ± 1.06	17.15%	P<.05
	15 min	36.20 ± 1.02	20.13%	P<.05
	20 min	36.47 ± 0.99	21.02%	P<.05
	25 min	36.60 ± 0.99	21.46%	P<.05
	30 min	36.57 ± 0.97	21.35%	P<.05
	35 min	36.57 ± 0.98	21.35%	P<.05
	40 min	36.60 ± 0.97	21.46%	P<.05
	45 min	36.57 ± 0.98	21.35%	P<.05
	50 min	36.50 ± 0.97	21.46%	P<.05
	55 min	36.57 ± 0.98	21.35%	P<.05
	60 min	36.60 ± 0.97	21.46%	P<.05

*Minute ventilation was kept constant at 100 ml/kg/min and intra-abdominal pressure 13-15 mmHg during study.

*Data are Mean ± SEM, P < 0.05 as compared with time 0.

**Figure 1: The Graph showing changes in PETCO₂ during CO₂ Pneumoperitoneum for laparoscopic Cholecystectomy (n=50)****Table 3: Changes in Arterial Blood Pressure during CO₂ Pneumoperitoneum for laparoscopic Cholecystectomy (n=50)**

	Time	Systolic BP MmHg	% >	Diastolic BP MmHg	% >	Mean BP MmHg	% >	P-Value
Before beginning of intra-abdominal CO ₂ insufflation	0 min	117.33 ± 2.49		77.29 ± 1.68		89.92 ± 1.70		
After beginning of intra-abdominal CO ₂ insufflation	5 min	124.00 ± 4.26	5.06%	82.57 ± 2.89	7.06%	96.71 ± 3.24	7.55%	P<.05
	10 min	131.96 ± 5.37	12.46%	88.50 ± 3.35	14.50%	102.00 ± 3.99	13.44%	P<.05
	15 min	134.25 ± 5.24	14.42%	89.71 ± 3.06	16.06%	104.63 ± 3.71	16.36%	P<.05
	20 min	136.54 ± 5.10	16.37%	89.92 ± 2.86	16.33%	104.92 ± 3.41	16.68%	P<.05
	25 min	137.88 ± 4.28	17.51%	90.54 ± 2.82	17.14%	106.71 ± 3.31	18.67%	P<.05
	30 min	135.75 ± 4.55	15.70%	89.71 ± 2.95	16.06%	105.29 ± 3.39	17.10%	P<.05
	35 min	133.67 ± 4.24	13.92%	88.29 ± 2.48	14.23%	103.67 ± 3.06	15.29%	P<.05
	40 min	131.58 ± 3.23	12.14%	87.63 ± 2.18	12.37%	101.50 ± 2.51	12.88%	P<.05
	45 min	130.00 ± 2.91	10.80%	85.79 ± 2.15	11.00%	101.04 ± 2.23	12.37%	P<.05
	50 min	127.38 ± 2.61	8.56%	84.63 ± 1.88	9.49%	100.33 ± 2.15	11.58%	P<.05
	55 min	129.83 ± 2.51	10.65%	85.71 ± 1.89	10.89%	99.88 ± 2.04	11.08%	P<.05
	60 min	129.58 ± 2.67	10.44%	84.96 ± 1.98	9.92%	100.38 ± 2.12	11.63%	P<.05

*Intra abdominal pressure was kept 13-15 mmHg during study.

*Data are Mean ± SEM, P < 0.05 as compared with time 0.

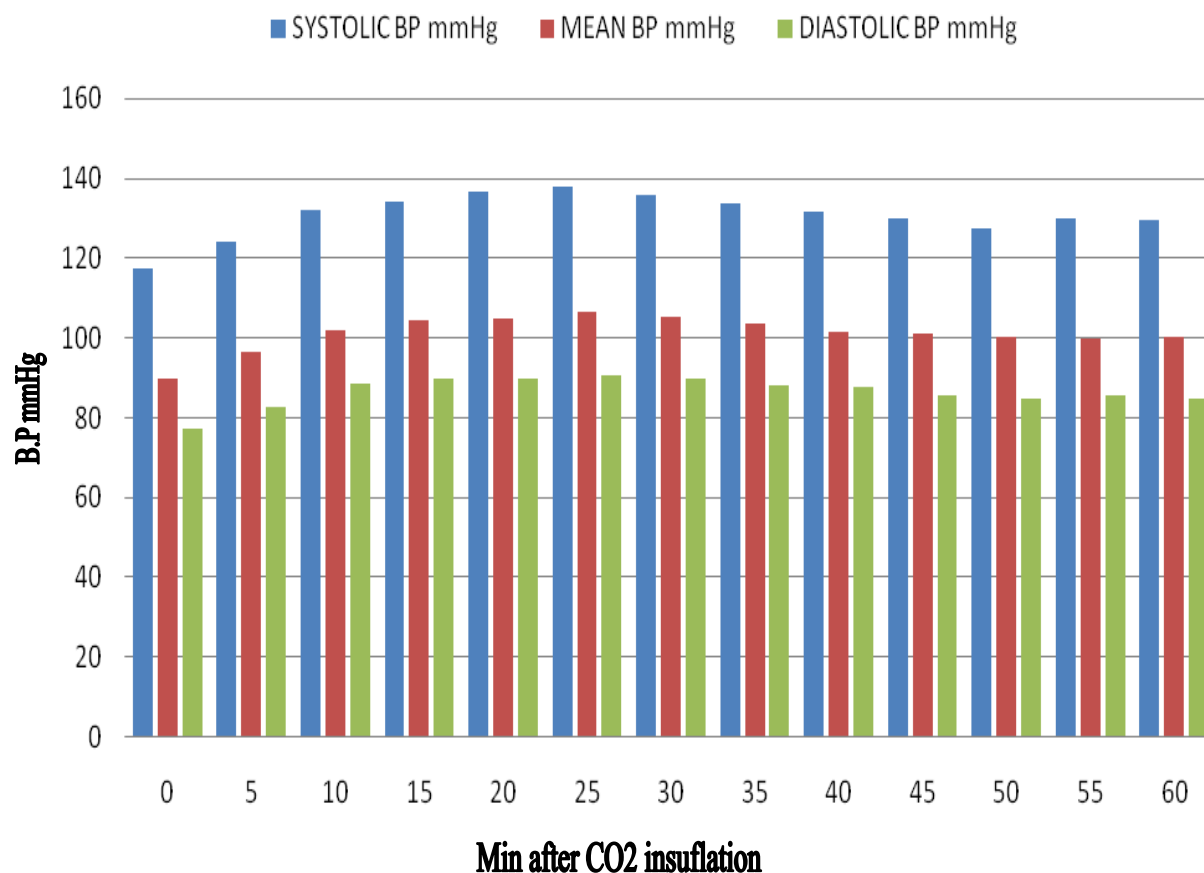


Figure 2: The Graph showing Changes in Arterial Blood Pressure during CO2 Pneumoperitoneum for laparoscopic Cholecystectomy (n=50)

Table 4: Changes in Heart Rate during CO2 Pneumoperitoneum for laparoscopic Cholecystectomy (n=50)

	Time	Heart Rate /min	% Change
Before beginning of intra-abdominal CO2 insufflation	0 min	86.58± 2.73	
After beginning of intra-abdominal CO2 insufflation	5min	86.29± 2.30	-0.34%
	10 min	87.17± 2.94	0.67%
	15 min	87.83± 2.83	1.44%
	20 min	91.00± 3.06	5.10%
	25 min	90.42±3.06	4.43%
	30 min	91.17± 3.39	5.29%
	35 min	89.67± 3.59	3.56%
	40 min	90.38± 3.41	4.38%
	45 min	90.38± 3.55	4.38%
	50 min	87.75± 3.47	1.35%
	55 min	86.67± 3.09	0.10%
	60 min	87.21± 3.19	0.72%

*Data are Mean ± SEM.

DISCUSSION

Effects on Etco2

The CO2 pneumoperitoneum produces increased intra abdominal pressure and increase in end tidal CO2 levels due to CO2 absorption from peritoneal cavity (6). During uneventful CO2 – pneumoperitoneum, PETCO2, and PaCO2 progressively increases to reach a plateau 15 to 30 min after beginning of CO2 insufflation in patients under controlled mechanical ventilation during gynaecological laparoscopy in the Trendelenburg position or laparoscopic cholecystectomy in head up position (7). The mean Pa CO2 and PETCO2 gradients do not change significantly during peritoneal insufflation of CO2. In our study PETCO2 levels increased progressively to 10% (33mmHg) of baseline (30mmHg) after 5 min, 17% (35mm Hg) after 10 min and plateau 21% (36mm Hg) after 20 min beginning of intra abdominal CO2 insufflation. The 21% increase in ETco2 levels remained elevated during period of intraabdominal CO2 insufflation. The 21% increase in ETco2 (36mm Hg) of base line (30mmHg) is found during CO2 pneumoperitoneum for laparoscopic

cholecystectomy under controlled mechanical ventilation at a constant minute ventilation 100ml/Kg/min and 13-15mmHg intra-abdominal pressure (Fig.1. and Table.2). The results of our study correlate with the previous study.

Absorption of CO₂ across the peritoneum is normally eliminated through the lungs because of its high aqueous solubility and diffusibility. If intraoperative ventilation is impaired, CO₂ absorption can result in hypercapnia and acidosis (8).

To prevent hypercapnia, close intraoperative monitoring of end-tidal CO₂ (ETCO₂) or arterial partial pressure of CO₂ (PaCO₂) is therefore essential. End tidal CO₂ (ETCO₂) is most commonly used as a non-invasive substitute for PaCO₂ in evaluating the adequacy of ventilation during laparoscopic surgery. The PaCO₂ usually correlates with the ETCO₂, except in patients with cardiopulmonary compromise and associated ventilation perfusion mismatch. A direct estimation of PaCO₂ may become necessary in such patients (9). In patients undergoing laparoscopic adjustable gastric banding, Demiroluk et al reported an increase in PaCO₂ levels from 34mm Hg at baseline to 42mm Hg after abdominal insufflation. In a study of laparoscopic versus open GBP (gastric by pass), ETCO₂ levels were found to increase by 14% of baseline (from 35 mm Hg to 40 mmHg), PaCO₂ levels increased by 10% of baseline (from 38 mmHg to 42 mm Hg) during laparoscopic GBP (10). In our study ETCO₂ levels are increased by 21% of baseline (from 30 mm Hg to 36 mm Hg) during laparoscopic cholecystectomy. (Fig.1, Tale 2.)

During pneumoperitoneum, appropriate ventilatory changes should be performed to eliminate the increased CO₂ load and prevent systemic acidosis. Ventilatory changes consist of increasing the minute ventilation. Dumont et al reported that minute ventilation increased by 21% to limit the rise in ETCO₂ in patients undergoing laparoscopic gastroplasty (11).

Elimination of the increased CO₂ load is performed primarily through the lungs. The total volume of exhaled CO₂ (VCO₂) during pneumoperitoneum is therefore an indirect method to quantify the amount of CO₂ absorbed during laparoscopy. In a study of nonobese patients, Tan et al estimated that the volume of CO₂ absorbed from the peritoneal cavity ranged from 38 to 42 ml/min during laparoscopy, which represented a 30% increase in the CO₂ load (12).

Effect on Blood Pressure and Heart Rate:

In our study 13-14% increase in systolic, diastolic and mean arterial blood pressure by base line is found 10 minutes after beginning of intra-abdominal CO₂ insufflation. The maximum 16-17% increase in systolic, diastolic and mean arterial blood pressure by baseline is observed between 20-30 minutes after beginning of

intra abdominal CO₂ insufflation. After 40 minutes 10% to 12% increase in systolic, diastolic and mean arterial blood pressure is observed during the period of CO₂ pneumoperitoneum. (Table 3. Fig 2.). The intra-abdominal pressure is maintained at 13-15mm Hg during CO₂ pneumoperitoneum. Cardiovascular changes have been characterized by many clinical studies. Most of these studies reported increased systemic and pulmonary vascular resistance and reduction of cardiac index when laparoscopy was performed at about 15mm Hg and head up tilt 10 degree. Joris et al (13) using invasive monitoring, observed a significant increase in mean arterial pressure (35%) after peritoneal insufflations, along with an increase of systemic vascular resistance (65%).

The insufflation of gas into the peritoneal cavity can provoke arrhythmias. Their incidence is as high as 14-27% of laparoscopies (14) which is higher than open surgery. In our study no change or slight increase in heart rate is observed (Table 4). Sinus bradycardia is found only in one patient immediately after the beginning of intra-abdominal CO₂ insufflation. The incidence of arrhythmias is very low in our study. The anaesthesia technique and agents used during the study has minimum effect on haemodynamics. The blood pressure and heart rate is recorded 20 minutes after the induction of anaesthesia when adequate level of depth of anaesthesia is achieved. Haemodynamic alterations occur only when the PaCO₂ is increased by 30% above the normal levels. Mild hypercapnia causes sympathetic stimulation which results in tachycardia, increased systemic vascular resistance, systemic arterial pressure, central venous pressure and cardiac out put (15). An increase in the intra-abdominal pressure is most important factor contributing to circulatory instability during laparoscopy (16). Reflex increase in vagal tone due to excessive stretching of the peritoneum may produce bradycardia. The threshold pressure that has minimum effects on haemodynamic functions is < 12mm Hg. If the inflation pressures are increased > 15mm Hg, the insufflated CO₂ compresses both venous capacitance and the arterial resistance vessels. This produces rise in the systemic vascular resistance and pulmonary vascular resistance leading to an increased after load. The mean arterial blood pressure rises and cardiac out put falls (25-35%) (17).

These haemodynamic changes are well tolerated by healthy individuals, but may have deleterious consequences in patients with cardio vascular disease (18-20).

CONCLUSION

Altered physiology has been demonstrated during laparoscopic cholecystectomy CO₂ pneumoperitoneum produces rise in end tidal CO₂ (ETCO₂) levels and increase in arterial blood pressure during laparoscopic

surgery under general anaesthesia with controlled ventilation at 13-15 mmHg intra abdominal pressure. Heart rate increases slightly or there is no change in heart rate. The increase in end tidal CO₂ (ETCO₂) levels and hemodynamic changes are proportional to the increased intra abdominal pressure.

Maintaining intra abdominal pressure under 15mmHg reduces the incidences of these changes leading to minimal and transient consecutive organ dysfunction and without consequences for the outcome. It is the merit of the anesthesiology team to not let the pathophysiological changes transform into complications, and the surgeon has to be aware that a low insufflation pressure diminishes the pathophysiological responses and avoids most of the complications.

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Address for Corresponding Author:

Brig. (R) Noor Hussain,

Professor of Anesthesia,

Foundation University Medical College,

Rawalpindi.

Original Article

Management of Iatrogenic Ureteral Injuries Analysis Report at Urology Department, Nishtar Hospital Multan

1. Asif Imran 2. Abid Hussain 3. Kishwar Naheed 4. M. Naveed Anwar

1. Sen. Registrar of Urology, NMC/NH, Multan 2. Assoc. Prof. of Surgery, MM&DC, Multan
3. Sen. Reg. of Obst. & Gynae, MM&DC, Multan 4. M.O. (Resident) of Urology, NMC/NH, Multan.

ABSTRACT

Objective: To review the etiology, diagnosis and treatment of iatrogenic ureteral injuries.

Place and Duration of study: The study was carried out at Department of Urology, Nishtar Hospital, Multan from December 2007 to December 2010.

Patients and methods: A total of 24 adult patients were included in the study. All patients were evaluated in terms of clinical presentation, physical examination and investigations. Different techniques including open repair and endoscopic maneuvers were performed as treatment modalities for ureteric injuries.

Results:- Out of 24 patients, 13 patients were female and 11 patients were males. Age of patients ranged from 20 years to 60 years. Out of 13 female patients, eleven developed lower ureteral injuries secondary to obstetrics and gynaecological procedures. Remaining two female patients had ureteral injuries following ureteroscopy for lower ureteral stones.

Eleven female patients had different symptoms including partial or total incontinence of urine, flank pain, symptoms of UTI, high grade fever, sepsis, anuria and urinary leakage. Patients who underwent URS or URS in situ lithotripsy had lower ureteral stones. Most of them had lumbar pain, symptoms of UTI, frequency, urgency and difficulty in micturition. Two patients had retention of urine for which they were catheterized. One had broken segment of DJ stent. Different techniques were employed, ureter re-implantation for distal ureteral injuries was performed in ten patients. For minor lacerations and suspected urinary leakage following URS for stone disintegration at lower ureter, ureteric catheter or DJ stent was placed.

Conclusion: Iatrogenic uretral injuries are rare following gynaecological, obstetrical and endourological procedures but are liable to occur due to inherent anatomic factors. Prompt diagnosis and institution of appropriate corrective surgical procedures often result satisfactory outcome.

Key Words: Iatrogenic, URS, Insitu lithotripsy,

INTRODUCTION

Ureteric injury is one of the most serious complications of gynaecological operations in the pelvis. It has a frequency ranging from 0.5% to 1.5% for all major pelvic operations.¹ Some other studies report gynaecological surgery as the traditional cause of more than 50% of iatrogenic injuries, followed by general surgical procedures.²

Recent data suggests that with the introduction of laparoscopic hysterectomy, ureteric injury rate has doubled from 0.3% to 0.7% since abandoning staples in favour of bipolar diathermy to secure uterine vascular pedicles.³ However in the last ten to fifteen years, with increase in complex minimally invasive endoscopic procedures being carried out by urologists for pyelo-ureteric disorders, for example URS + Dormia basket, disintegration of ureteric calculi now account for most of ureteric injuries.⁴ Most ureteric injuries are unsuspected and diagnosed postoperatively. Ureteral injuries consequent to gynaecologic surgery if

diagnosed intraoperatively, decrease postoperative morbidity, minimize loss of renal function and reduce subsequent need for nephrectomy. Early recognition also decreases the incidence of ureterovaginal fistula as compared to postoperative diagnosis with delayed repair.⁵ We report our experience in the management of twenty six iatrogenic ureteric injuries over three years period. We analysed the etiology, types of ureteric injuries and management on the final outcome of the injury.

PATIENTS AND METHODS

The present study includes twenty four patients treated for ureteric injuries due to variety of reasons, gynaecological, obstetric and following ureteroscopy for stone removal. The patients who had gynaecological surgery(Hysterectomy) for pelvic malignancy, previous pelvic irradiation and pelvic inflammatory disease were not included in the study. Median age of the patients was 35(Range 20-60) years.

About 11 patients were referred from peripheral hospitals. Nine of them were operated upon by qualified surgeons while two of them by inexperienced surgeons. Almost all patients underwent detailed history, physical examination, complete urine examination, urine culture and sensitivity, complete blood count, blood urea, serum creatinine and ultrasonography. Some patients also underwent intravenous urography. Antegrade pyelography and radioisotope study was carried out when indicated. Mean time since injury and presentation was about 3 weeks (Range 1 day-1 year).

Six patients had ureterovaginal fistula while two patients had complete bilateral ureteric obstruction. The cause of bilateral ureteric obstruction was found to be suture ligation.

Six patients developed mucosal injuries while four had ureteral perforations (Partial or complete). False passage was found in four patients. In one patient, ureteric avulsion occurred in an attempt to disintegrate lower ureteral calculi with in situ lithotripsy. Six patients developed mucosal injuries and false passages were seen in four patients. Four patients had ureteral perforations (partial or complete). These injuries were recognized intraoperatively. In cases of mucosal injuries, 4 – 6 Fr ureteric catheter was inserted to rest the ureter and facilitate healing. These catheters were removed 2 – 3 days later in the ward. One patient with small mucosal injury did not require urological intervention and was treated conservatively. In patients with ureteric perforations, DJ stent was placed for about one month and then removed. In one patient, ureteric avulsion occurred following URS that was recognized and ureteroneocystostomy was carried out at the same time. Six patients who had ureterovaginal fistula underwent ureteroneocystostomy with stent insertion to promote healing and secure patency. In three lower ureteric injuries where segment of lower ureter was nonviable, ureteroneocystostomy with Boari flap formation was undertaken. One patient with partial urinary incontinence, only stent was placed and fistula resolved within four weeks. One patient developing unilateral ureteric ligation of ureter underwent PCN.

Two patients referred from peripheral hospitals had bilateral ligation of lower ureter and they presented with anuria. One patient was stable enough to proceed for exploration and ureteroneocystostomy was performed with Psoas hitch to ensure tension free anastomosis. The other patient who had severe renal impairment due to ureteric obstruction was hemodialysed and later on ureteroneocystostomy was performed.

RESULTS

There were twenty six iatrogenic ureteral injuries in 24 patients during the three years period. The majority of injuries were caused by urological procedures especially lithoclastic disintegration of ureteric calculi

and other ureteroscopic procedures. Table 1 shows the causes of iatrogenic injuries in this series. Eleven patients developed ureteric injuries consequent to gynaecological and obstetrical surgery. Two patients on ultrasonography and clinical assessment had bilateral ureteric obstruction. Table 2 shows the types of ureteric injuries encountered. One serious complication occurred was ureteric avulsion that required reconstructive surgery i.e. ureteroneocystostomy with Boari flap formation. Major reconstructive treatment offered included ureteroneocystostomy with Psoas hitch in eight lower ureteric injuries. In three patients, Boari flap formation was carried out. One patient showed spontaneous resolution of lower ureteric obstruction on PCN contrast study. Ureteral minor injuries including mucosal, small perforations and false passages were managed by DJ stent insertion or ureteric catheter placement. In follow up of these patients, no residual hydroureter and hydronephrosis were seen. In one patient with UVF, there was continuous leakage of urine after uretero-neocystostomy. So, re-exploration and Boari flap formation was undertaken. Two patients had respiratory tract infection that settled with treatment. Table 3 & 4 summarize the treatment and outcome of treatment of the ureteric injuries.

Table 1: Causes of iatrogenic Ureteral injuries

Types	Number	Percentage
Obstetrics and gynaecologic surgery	11	42%
Abdominal Hysterectomy	08	
Cesarian Section	03	
Urological Surgery	15	58%
Lithoclast	07	
Ureteroscopy	03	
Dormia Basket	03	
Insertion of "J" stent	02	

Table 2: Types of Ureteric injuries

Nature	Number	Percentage
Injury to mucosa	06	23.0%
Perforations (complete or partial)	04	15.5%
Ureteric avulsion	01	4.0%
False passages	04	15.5%
Ureterovaginal fistula	06	23.0%
Ureteric ligation	05	19.0%

Table 3: Treatment of Iatrogenic Ureteral Injuries

Treatment	Number	Percentage
DJ stent insertion/ureteric catheter placement	13	50%
PCN	01	4%
Psoas hitch	08	31%
Boari Flap	03	11%
Spontaneous resolution	01	04%
Total	26	100%

Table 4: Outcome of Management of Ureteric Injuries

Outcome	Number	Percentage
Successful resolution	25	96.2%
Ureteric stricture	01	3.8%

DISCUSSION

Ureteric injuries are among the most important complications associated with the major pelvic gynecologic surgery. Most of these injuries occur in distal portion of the ureter where it passes beneath the uterine vessels. Other common sites are the area of ureterovesical junction and the base of infundibulopelvic ligament⁶. Any gynaecological procedure can cause ureteric injury but abdominal hysterectomy is the most common procedure associated with ureteric injury. The rate of bilateral ureteric injury is increased when it is performed for malignancy, conditions causing induration and distortion of pelvic anatomy for example huge fibroid or previous pelvic inflammatory disease⁷.

In the present study ureteric injuries occurred consequent to gynaecological surgery done for benign conditions. Eleven patients were referred from peripheral hospitals where surgery had been performed by inexperienced surgeons. Ureteric injury following gynaecological procedures is due to entrapment or ligation of the ureter by a suture. Intra-operative bleeding with difficult hemostasis is pre-dominant risk factor contributing to the injuries. However in 4 out of 11 cases, referring gynaecologists described the operation as routine. This is consistent with the literature where half of the injuries had no identifiable pre-disposing factors⁸. Some patients present with pain, fever and vaginal discharge⁹. Patients who develop bilateral ureteric injuries present with oliguria or anuria. In the present study, pre-dominant symptoms were urinary incontinence, loin pain and anuria in patients complicated from gynaecological surgery. Ureteric injury may be recognized intra-operatively. Short defects may be managed by end to end anastomosis. For larger defects ureteroneocystostomy with stent placement gives good results. Sometimes Boari flap can be used to bring the bladder close to the cut end of the ureter¹⁰. Psoas hitch procedure can be used where flap is not rotated. These bladder reconstructions help to achieve tension free ureteroneocystostomy.

Intra-operative recognition and repair of ureteric injury is paramount to avoid and repair the permanent damage associated with unrecognized injuries but most of the injuries are unsuspected and diagnosed post-operatively¹¹. In the present study, the diagnosis was made post-operatively. If the diagnosis is made post-operatively, then either endoscopic or open surgical procedure can

be carried out. If the extent of injury is in question or for minor injury, retrograde ureteric stents can be placed. Other endoscopic procedures include balloon dilatation, endo-uretrotomy with cold knife or hot electrode. When a stent placement is possible, as many as 73% of the patients will not require open surgery¹². Some authors suggest stent placement or percutaneous nephrostomy as the first line of therapy¹³, others recommend open repair. Where open surgery is needed, the timing of repair has been debatable. Recent studies suggest similar outcome after immediate and delayed repairs¹⁴.

Prevention of the ureteric injury should be the primary aim during major pelvic surgery. All necessary precautions should be undertaken, including careful dissection and recognition of the ureters¹⁵. Some investigators have suggested the role of prophylactic ureteric stenting but studies fail to show decreased incidence of ureteric injuries. In some patients early identification of ureteric injury is possible with use of stents. According to recent data, ureteric injuries also result at laparoscopic hysterectomy due to surgical inexperience and technique development¹⁶. In Codrane review, it was found that ureteric injury rate was higher with laparoscopic hysterectomy than the abdominal hysterectomy¹⁷.

With greater use of the minimally invasive techniques in urology, the incidence of ureteric injury has increased. This view has been confirmed by findings in this study. Ureteroscopy is now-a-days one of the techniques most widely used for upper tract pathology. Studies show different ureteric injuries like mucosal injury, false passages, bleeding, ureteral perforations and ureteric avulsion as intra-operative complications¹⁸. In the present study, these injuries were also seen as intraoperative complications following lithoclast disintegration of ureteral stones, URS as diagnostic procedure and stent insertion.

Treatment options for ureteric injuries in this series included ureteric catheter placement or J stent insertion in cases of ureteric mucosal injury, ureteric perforations and false passages. As reported by others and our experience in this study, most of these injuries healed without any serious sequelae¹⁹.

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Address for Corresponding Author:

Asif Imran,

Senior Registrar of Urology,

NMC/NH, Multan.

Original Article

An Epidemiologic Profile of Homicidal Deaths in Karachi

**1. Romela Naz 2. Imran Afzal 3. Imran Jawad 4. Muhammad Iqbal Mughal
5. Afshan Kamran**

1. Asstt. Prof. of Forensic Medicine and Toxicology, Sir Syed CMS, Karachi 2. Assoc. Prof. Forensic Medicine, M&DC, Karachi 3. Assoc Prof. of Forensic Medicine, UCM, University of Lahore 4. Prof. of Forensic Medicine, Central Park MC, Lahore 5. Asstt. Prof. of Pharmacology, Altamash Dental College, Karachi

ABSTRACT

Objective: The study was planned to review the epidemiologic profile of homicidal deaths in Karachi.

Design of Study: Observational study.

Duration and Place of Study: Since Jan. 2009 to June 2009 and place of study was the Department of Forensic Medicine and Toxicology of Jinnah Postgraduate Medical Centre (JPMC), Karachi.

Materials & Methods: Two hundred and ninety seven cases were included in the study. The data was collected by reviewing the police papers and autopsy reports. The parameters recorded were age, sex, manner of death, type of weapon used, part of the body involved, time of death and location of fatal wound.

Results: During the study period there were 297 cases of homicides, out of which 259 (87.2%) were firearms related homicides and majority of victims were males (75.4%) and most of them were between 21 to 30 years of age (39.5%). Most of the crimes occurred during night hours (59.5%) and head injuries were most common (49.8%).

Conclusions & recommendations: The firearms related homicides are highest in number, the reason being easy access to firearm weapons. Further studies and effective intervention strategies are needed to be employed to reduce the occurrence of homicides. The situation demands a strict control on firearms by government.

Key words: Homicidal, Fire arms, Blunt weapon, Sharp weapon, Hanging and Strangulation.

INTRODUCTION

Crime is something that impacts everyone whether directly or indirectly through societal and economic costs and the leading causes of crime are jealousy, love, revenge, poverty, hatred, desperation, juvenile thrills, lack of education, broken home and “gang” or peer pressure.

The major form of crime is murder or killing of another person (homicide) in which the main causes are target killings (very common in Karachi nowadays), deeply rooted psychological problems, too much stress, isolation, bad parenting etc. Look at the first murder known man which was when Kane killed Abel because he was jealous that God likes Abel’s flowers more than his.

The World Health Organization (WHO) defines homicide as “any death resulting from injury purposefully inflicted by another person”. This is crime is unacceptable to all types of society.¹ The world witnesses over 500,000 deaths due to homicide annually.²

It is the most heinous crime against society and like other parts of the world it is very common in our country.^{3, 6} In spite of legal controls, homicidal deaths are on rise.^{3,4}

There has been a tremendous increase in the number of fire-arm related homicide in childhood and adolescence

(CDC 2004).⁵ There is a positive co-relation between homicide rates and availability of guns in developed nations (Hemenway and Miller 2000). The number of firearms in the hands of private citizens continues to grow each year at a rate far exceeding that of the population as a whole.

MATERIALS AND METHODS

This study was undertaken in the department of Forensic Medicine and Toxicology of Jinnah Postgraduate Medical Centre (JPMC) Karachi from January 2009 to June 2009 on victims of homicidal deaths. This centre is an apex medical centre where 75% of all medico legal autopsies in Karachi are performed. The data was collected by reviewing the police papers and autopsy reports. The parameters recorded were age, sex, manner of death, type of weapon used, part of the body involved, time of death and location of fatal wound.

RESULTS

During the period of our study there were 297 cases of homicidal death. The cases where the manner of death was undetermined were not included in the study. Out of these 297 cases, 224 (75.42%) were males and 73(24.58%) were females. (Table No. 1)

Table No.1: Sex distribution in homicidal deaths (n=297)

Sr. No.	Sex	Number of cases	Percentage
1	Male	224	75.42
2	Female	73	24.58
	Total	297	100.00

There were 4(1.34%) cases below 10 years of age, 21(7.07%) cases in 11-20 years group, 117(39.39%) cases in 21-30 years age group, 89 (29.97%) cases in 31-40 years age group, 31 (10.44%) cases in 51-60 years age group, 22(7.41%) cases in 51-60 years age group, 13 (4.38%) cases in age group above 60 years. The majority of cases fall in 3rd decade. The next common age group was 4th decade. (Table No. 2)

Table No.2: Age distribution of the victims (n=297)

Age group	Number of cases	Percentage
0-10 years	4	1.34
11-20 years	21	7.07
21-30 years	117	39.39
31-40 years	89	29.97
41-50 years	31	10.44
51-60 years	22	7.41
61 onwards	13	4.38
TOTAL	297	100.00

The firearms were used in maximum number (87.21% cases). Blunt means were used in 5.05% cases, sharp weapon in 2.02% cases, hanging & strangulation in 3.70% cases & burns in 2.02% cases. (Table No. 3)

Table No. 3: Weapon used in homicidal deaths (n=297)

Types of weapon	Number of cases	Percentage
Firearms	259	87.21
Blunt weapon	15	5.05
Sharp weapon	06	2.02
Hanging & strangulation	11	3.70
Burns	06	2.02
Total	297	100.00

Head & neck are maximally hit area in all forms of violence, 49.81 % cases of firearms, 83.33% cases of sharp weapons and 80.00% cases of blunt weapons. The chest was involved in 31.26% cases of firearms, 16.67% cases of sharp weapon and 20.00% cases of blunt weapon. The abdomen, lower limb and upper limbs were hit in firearm cases respectively 6.94%, 6.20% & 5.79% cases. (Table No. 4)

Table No. 4: Part of body involved in fatal injuries.

Area involved	Firearms cases(%age)	Sharp cases (%age)	Blunt cases (%age)
Head and neck	129 (49.81%)	05(83.33%)	12(80.00%)
Chest	81 (31.26%)	01(16.67%)	3(20.00%)
Abdomen	18 (6.94%)	0	0
Upper Limb	15 (5.79%)	0	0
Lower Limb	16 (6.20%)	0	0
Total	259	6	15

In about 60 % cases the time of homicidal deaths was evening / night. (Table No. 5)

Table No. 5: Time of homicide.

Time	Number of cases	Percentage
6pm – 6am	177	59.60
6am – 6pm	120	40.40
Total	297	100.00

DISCUSSION

In our study majority of homicidal cases are males. Criminal behavior also breaks down along gender lines, males are more likely, both historically and sociologically to be responsible for a criminal behavior. In part this may be explained by hormonal differences, the testosterone being a hormone linked to more violent and risky behavior. Certain aspects of male social behavior may also encourage this, such as the need to appear “tougher” which helps legitimize violence. Age is often a large determinant of criminal behavior; most initial offenders tend to be younger. Criminal activity then decreases as age increases; this may be a result of other social responsibilities precedence such as taking care of a family.

Most of the victims belonged to their third decade of life. These finding are consistent with that of other studies in Pakistan^{8,9,10} which gives the highest incidence in the same age group and 28-40% of all homicides in the age bracket of 20-29 years.^{5,11,12,13,14,15} but differ from the findings of Chu and Rachuba et al as they have reported 15-19 years and 10-25 years as the most vulnerable age group in their respective studies^{16,7} The number was lower at the extremes of age as children below ten and adults above sixty were involved in only 1.34% and 4.3%. Wilkey and others have also reported this low incident at the extremes of age.¹⁸

Gun related violence is most common and in conjunction with target killings and gang violence often involving young adults. In our study the firearms were the major weapon of offence (87.21%) & it is consistent with other studies in Pakistan^{11,15,25} and in consensus

with a high level of firearms possession.¹⁶ It is followed by deaths due to application of blunt weapons (5.05%) and asphyxiation (3.70%). This is in contrast to the studies conducted in New Found land and Costa-Rica^{19,20} where sharp weapons pre-dominate as the most common method of homicide. This is because firearms are not freely available and law is strict relating to the possession of firearm weapons.²¹ In the United States, firearms are used in more than 60% of all homicides.²⁶ Death due to head injury was the commonest finding followed by the chest which is consistent with the findings of others.^{22,23} The upper limbs and lower limbs sustained minimum number of fatal injuries. When firearms are used head and neck are most commonly involved, when blunt object is used in most of the cases face and head was the target but when sharp object was used, head, neck and abdominal regions were commonly involved.

In the present study, it has been observed that offence can occur at any time of the day. The highest incidence was observed during evening and night. Others had similar findings.²⁴

CONCLUSIONS

The firearms related homicides are highest in number, the reason being easy access to firearm weapons. Further studies and effective intervention strategies are needed to be employed to reduce the occurrence of homicides. The situation demands a strict control on firearms by government.

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Original Article

The Effect of Neem (*Azadirachta Indica*) Leaf Extract and Neem Compound Nimolicine On Gastric Acidity

1. Qamer Aziz Siddiquie 2. Syed Naim ul Hassan Naqvi 3. Mirza Mohammad Feisal Subhan 4. Syed I H Zaidi

1. Assoc. Prof. of Physiology, Baqai Medical University, Karachi 2. Prof. of Pharmacy, BMU, Karachi
3. Asstt. Prof. of Physiology, CM&MS, Arabian Gulf University, Manama, Kingdom of Bahrain
4. Col. ® Pakistan Army, PNS Shifa Karachi.

ABSTRACT

Objectives: This study has been conducted to look at the anti acid effect of Neem and to compare the effect of leaf extract with the pure compound nimolicine on the gastric acidity. Nimolicine has been studied for its anti acid effect for the first time.

Design of Study: Experimental study.

Place of Study: This study was conducted in the department of Physiology, Baqai Medical College and the Department of Pharmacology in Baqai Institute of Pharmaceutical Sciences, Karachi.

Materials and Methods: Ethanol induced gastric ulcers in albino rats were treated with methanolic neem leaf extract (800mg/day for 5 days) and nimolicine (1%/day for 3 days) and the gastric acid secretion was estimated. The control of the treated group was given peanut oil 1 ml/day for 5 days. The effect on gastric secretion was compared with the effect of anti-ulcer drugs cimetidine® (50 mg/kg for 7-10 days) and omeperazole® (2.5 mg/kg/day for 7-14 days).

Result: Neem leaf extract is a better suppressor of H-ion secretion compared to nimolicine but both neem leaf extract & nimolicine did not show a significant suppression of acid compared to ranitidine and omeperazole. The comparison between control and ranitidine in suppression of acid was significant.

Conclusion: Methanolic NLE and neem compound nimolicine do not decrease gastric acidity and their role as anti-ulcer agents may be because of other mechanisms which need to be studied.

Key words Acid peptic disease, *Azadirachta indica*, anti ulcer, nimolicine.

INTRODUCTION

Acid peptic disease is a common clinical problem. About 4 million people suffer from this disease in the USA. The current therapy for the disease has limitations and not easily affordable. Thus alternate herbal preparations are gaining popularity. Neem (*Azadirachta indica*) has been claimed to have an anti ulcer effect but the mechanism is still not clear. Food after chewing is swallowed into the stomach which stores, mixes and empties the chyme into the duodenum. The gastric secretion contains HCl which is responsible for the maintenance of acidic pH. A powerful defensive mechanism is provided by mucus bicarbonate layer which serves as a mucus gel impeding diffusions of harmful substances maintaining the integrity of mucosal membrane^{1, 2}. A net imbalance in mucosal offensive and defensive factors play a major role in ulcer production³. PG plays a central role in providing this defense⁴. Peptic ulcer disease (PUD) is a mucosal erosion equal to or greater than 0.5 cm of an area in the stomach or duodenum. The life time risk of developing PUD is 10%⁵. The use of anti-ulcer drugs, though they are effective has limitations⁶⁻⁹. Thus recent interest has been towards non toxic herbal preparations

which is increasing⁴. *Azadirachta indica* (neem) is an important plant of great medicinal importance and has been shown to posses anti-ulcer and anti secretory effects¹⁰⁻¹⁵. Thus in this part of the study the effects of methanolic extract of neem leaves and isolated compound of neem Nimolicine (NC) on gastric acidity have been seen while demonstrating the anti-ulcer effects of neem leaf extract NLE and NC. The anti secretory effects of NLE and NC have been compared with cimetidine and omeperazole. The anti secretory effects of NC have been studied for the first time. Nimolicine (*Azadiradione*) was isolated from the fresh fruit coatings in 0.35% yield (calculated according to the weight of fresh coatings)¹⁶.

MATERIALS AND METHODS

Male and female Sprague Dawley rats weighing 180-200 Gms. were used. They were purchased from the animal house of HEJ Institute of Chemistry, Karachi University. They were kept in the animal house of Baqai Medical University under optimum conditions and temperature ranging from 20 to 22 °C. The animals were kept in plastic cages and were acclimatized to laboratory conditions and had free access to food and

tap water ad libitum. For weighing of rats an electronic computerized talking weighing machine (Toyo model AT-1020, Japan) (1 to 5000 Grams or 11 lbs.) was used. Animals were fasted for 48 hrs. with water ad libitum before each experiment. During this period rats were transferred in wired cages where the floor was wired to prevent coprophagy. This was done to ensure an empty stomach. The rats were divided into six experimental groups i.e. each group comprised of ten rats i.e., five males and five females. Ulcer induction in Group-1 was done by per oral administration of 1ml of 100% ethanol and the rats were sacrificed after 24 hrs. The other groups each (n=10) were the experimental groups received oral doses of Neem extract/ Neem compounds/ standard ulcer healing drugs as shown in tables. In each test group one control were kept. The control group was given Peanut oil 1 ml/day for 7 days. The test groups received oral NLE 1ml/day (0.88 gm) for 5 days and NC 1%/ day for 3 days (0.01 gm in 1 ml). The H-ion secretion was compared to the effects of oral ranitidine 50 mg/kg per day for 5 days and oral omeperazole 2.5mg/kg per day for 10 days. We used the curative method of treatment instead of protective method as done by most other workers.

Neem leaf extract and neem compound nimolicine NC was obtained from HEJ by the courtesy of Prof. Dr Beena S. Siddiquie. NC in pure powder form. Dissection of animals was carried out according to the protocol for each group. Chloroform was used to anaesthetize the rats. The animals were placed in a glass dessicator containing cotton swabs soaked in chloroform (CHCl₄) for a few minutes. The rat was then placed on a dissection board and immobilized by paper pins. A midline incision was given and the stomach was exposed. The upper and the pyloric ends were ligated so that the contents do not escape. The stomach was removed and opened along the greater curvature. Gastric contents were collected and gastric acidity was determined as described (17).

Calculation of gastric acidity

The gastric contents were drained into a centrifuge tube and centrifuged for 1 hour at 45 cycles per second. The supernatant was then collected in a test tube. The volume measured by a 0.5 ml pipette was (V₁). This was titrated with NaOH (N₂=0.1M or 0.40 gms in 100ml. of distilled water) by a 10 ml burette to an end point using Phenolphthaleine as an indicator. The NaOH volume (V₂) consumed during titration was used for calculation. The H-ion secretion was expressed as $\mu\text{Eq./100gm}$.

The study was approved by the Board of advanced study and the ethical committee of Baqai Medical University. There was no funding from external or internal resources.

Statistical analysis of data

The computerised software programme SPSS version 18 was used for the analysis of data. The results were obtained by applying a one way analysis of variance (ANOVA). The significant p value was considered to be ($p < 0.05$). Bonferroni correction was used to reduce type-one error.

RESULTS

Gastric Secretion of H-ion ($\mu\text{Eq}/100\text{ gms}$)

The Mean values with $\text{SE} \pm$ of H-ion ($\mu\text{Eq}/100\text{gm}$) secretion in the control group and the treated group is shown. The pair wise comparison of different groups has also been shown. There is a significant difference ($p < 0.05$) on comparison of control group with the ranitidine group (Table-8). The other values are insignificant indicating that the anti secretory effects of NLE and NC as compared to ranitidine® (Ran) and omeperazole® (OMP) are not of importance statistically though the values apparently differ.

Table-1. Mean \pm SE of weight and gastric secretion of H-ions ($\mu\text{Eq}/100\text{ gms}$) in check, control and test groups.

Group	Wt (gms)	SE \pm	H ($\mu\text{Eq}/100\text{ gms}$)	SE \pm	N
Check (Ethanol 100%)	161.09	10.26	1.32	0.04	7
PNO (1ml) (control)	202.31	7.26	6.36	1.42	14
Ran (50 mg/kg)	222.86	13.62	0.38*	0.1	5
OMP (2.5 mg/kg)	213.33	6.15	2.08	0.13	6
NLE (1ml/day)	189	7.14	4.03	0.7	8
NC (1% sol)	231.67	30.6	5.19	0.47	9

* Significantly different from the control ($p < 0.05$)

DISCUSSION

Treatment of ulcers is a global problem and needs to be studied in detail specially whether an over secretion of H-ions is the basic cause of ulcers. The treatment of ulcers is aimed at reducing acid secretion. The present study was conducted to look at the anti H-ions secretory effects of methanolic neem leaf extract (NLE) and a newly isolated neem compound nimolicine (NC). In this study the gastric secretion of H-ions ($\mu\text{Eq}/100\text{gm}$) in the treated group is lesser compared to the control group but the result is not statistically significant. Significant suppression of H-ion secretion is only of ranitidine showing values of 0.38 ± 0.09 . The result of

this study is different from another study where they have shown a dose dependent reduction of gastric acidity augmented by cimetidine indicating a possible H₂-receptor blockade effect¹⁵ of aqueous extract of neem leaves.

The effects of aqueous extract of neem leaves have also been shown to have an anti-ulcer effect by preventing mast cell degranulation and increasing the amount of adherent gastric mucus in stressed animals¹². The present study differs in results because of the difference that the methanolic extract is different from the aqueous extract of neem leaves. Methanolic extracts are more soluble compared to aqueous extract and are therefore more effective. Mast cells by secreting histamine are responsible for stress induced ulcers but the mechanism of ulcers induced by ethanol is different³³.

It has been shown that the neem (*Azadirachta indica*) bark extract inhibits H⁺-K⁺-ATPase activity in vitro, prevents mucus depletion and causes mast cell degranulation but provides gastroprotection by its significant antioxidant effect. Bark extract was shown to be equipotent to ranitidine but more potent to omeperazole in inhibiting pylorus ligation induced acid secretion. It also inhibits MMI (mercapto-methylimidazole) induced acid secretion which acts through histamine release¹⁰. The potent anti-ulcer and anti secretory effect of Neem Leaf extract has been attributed to a glycoside¹⁸ which inhibits Cl⁻-transport in the gastric epithelium¹⁹.

The effect of neem bark extract on gastric acidity showing a reduction in gastric volume and pepsin activity in a clinical trial¹⁴ is different from the present study because the bark extract is different in composition compared to leaf extract²⁰. The anti-ulcer effect of methanolic extract of neem leaves and NC may be due to their antioxidant effect rather than anti secretory effect.

The present study also differs from the effects of Nimbidin (80 mg/Kg) significantly inhibiting histamine induced DU in guinea pigs²¹. This possibly demonstrates the H₂ receptor blocking effect of Nimbidin which may not be the mechanism involved in anti-ulcer effect of NLE and NC²²

The lack of significant results of NLE and NC on gastric acidity possibly explains that the mechanism of ulcer inhibition may be due to other reasons. Similar findings have been shown²³ regarding gastroprotection provided by omeperazole was because of its antioxidant and anti apoptotic role. Development of gastric ulcers is a multifactorial process²³ where a balance between acid production and bicarbonate-mucus barrier is disturbed²⁴. A disturbance in the antioxidant system²⁵⁻²⁶ due to reactive oxygen species (ROS) is the major causative factor^{27, 28} which develop due to neutrophil infiltration²⁹. Non-ROS-mediated apoptotic cell death occurs in stress ulcer through the involvement of NO³⁰,

caspase-3³¹ and an imbalance between antiapoptotic Bcl-2 and apoptotic Bax proteins³². TNF- α -induced apoptotic cell death is also noted in ethanol induced gastric damage³³. Thus a good anti-ulcer agent must have anti secretory, anti inflammatory, anti oxidant and angiogenic effects. Neem is a well known plant having all these properties. But chemical composition of different parts of tree varies and may have different function and mechanism of action. The leaf extract differs in composition to bark extract ie nimbidine is present in bark extract not in leaf extract. The leaf extract containing azadirachtin (AZ) are 3-4 times more potent in effects compared to the pure isolated compound AZ³⁴. These differences in chemistry might be a factor in the difference in results shown in present study.

The financial impact of PUD is tremendous with an estimated burden on direct and indirect health care costs of ~\$10 billion per year in the United States⁴. Thus further clinical trials to prove the effectiveness of neem extracts must be conducted. This will prove to be a better and cost effective remedy for gastric ulcer therapy specially in the developing world.

CONCLUSION

Methanolic NLE and isolated compound of neem Nimolicine NC do not decrease gastric acidity and their role as anti-ulcer agents may be because of other mechanisms which need to be explored.

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Address for Corresponding Author:**Qamer Aziz Siddiquie,**

Assoc. Prof. of Physiology,
Baqai Medical University,
Toll Plaza, Karachi-74600
Cell No.0333-3145734

Original Article**A Unique Approach to Learning/Teaching Anatomy****1. Huma Musarrat Khan 2. Rohail M. Mirza 3. Farah Shahid**

1. Assoc. Prof. of Anatomy, FUMC, Rawalpindi 2. Student 3. Demonstrator/Lecturer of Anatomy, FUMC, Rawalpindi

ABSTRACT

Context: The present day teaching emphasizes on teaching methodologies that capture the interest of students and increase their satisfaction.

Objective: To assess the effectiveness of nontraditional teaching methodologies such as storytelling for teaching anatomy and to determine whether this method enhances student satisfaction.

Materials and Methods: The study was carried out in Foundation University Medical College, Rawalpindi (Pakistan) on first year MBBS students (n=87). The students were given a story, adapted from: "The case of the dividing cell: mitosis and meiosis in the cellular court" (http://www.sciencecases.org/mitosis_meiosis/mitosis_meiosis.asp) by Clyde Freeman Herreid. Copyright held by National center for case study teaching in science, University at Buffalo, state university of New York. Used with permission. The students were divided into small groups who discussed the learning issues in three interactive sessions, after which, they were given a surprise assessment test and an anonymous questionnaire which was to be answered on an open scale of 1-10 (1 being the minimum score and 10 maximum) regarding the effectiveness of this methodology.

Findings: Students enjoyed the sessions and would like similar sessions in future (mean evaluation score: $5.92/10 \pm 3.15$). An overall satisfaction score of 6.52 ± 1.75 was obtained. Mean of assessment results was $92.7\% \pm 10.4$. Some students felt that it was more time consuming as compared to lectures and could not be used to cover all topics.

Conclusion: Teaching anatomy by storytelling captured the interest of majority of the students who found it an effective teaching methodology. However, other traditional tools of teaching should also be an integral part of anatomy curriculum.

Key Words: Teaching methodologies, storytelling, teaching tool, teaching anatomy, student satisfaction, present day teaching.

INTRODUCTION

In the present age, teaching has become a multifaceted process that lays emphasis on teaching/learning methodologies which focus more on active and conceptual learning. This has become a serious challenge for teachers, and an effort is being made at all levels to supplement passive learning methods such as traditional lectures, with other methodologies that captivate students, increase their satisfaction and motivate active learning¹. One of such methodologies is the use of "case studies" or "stories". Case studies are stories analyzed through discussion, and used to achieve learning objectives in the classroom. Business and law schools have a long history of using real or simulated stories known as "cases" to teach students about their topic of discussion. Harvard University is among the pioneers in developing cases in these subjects², and has produced teachers who have carried this methodology to other institutions. However, case studies have rarely been employed in undergraduate science teaching except as stories or experiences told by an instructor as part of introducing or summing up a lecture. James B. Conant of Harvard was probably the first science educationalist to design and implement a

complete course around this teaching methodology. However, unlike the practice in other fields, where cases were presented as part of a discussion, Conant presented cases entirely in the form of a lecture. His style did not become popular, and was hardly ever used again in any institute³.

Teaching of anatomy is generally considered as an integral part of medical education; yet, it is normally taken as a subject full of hard core facts putting a lot of strain on rote memory⁴. This realization has created the need to deliver the subject of Anatomy in a more effective and efficient manner⁵. Moreover, as thinking is a deep desire of the human mind, a need is felt more acutely than ever to rescue anatomy from the mere status of dry, boring description of facts to living factual realities.

"Tell me a fact and I'll learn. Tell me the truth and I'll believe. But tell me a story and it will live in my heart forever." - Indian Proverb

With the advent of latest changes in the teaching methodology and introduction of modern medical education in Pakistani medical schools, a greater burden has been put on the faculty of anatomy to introduce newer teaching methodologies which are more interesting and captivating. Keeping this in mind a

study was planned in which the first year medical students of Foundation University Medical College, Rawalpindi (batch 2010) were exposed to sessions during which a “story” was used to induce learning. The case chosen was rather atypical as compared to the traditional “cases” in the sense that it was purely a fictitious and imaginary story which had little to do with the real world. It was unlike the cases normally used in business schools which reflect real life situations and was chosen specifically to capture the student interest rather than to recreate a true life scenario.

OBJECTIVE

The objective of the study was to assess the effectiveness of nontraditional teaching methodologies such as storytelling for teaching anatomy and to determine whether this particular teaching method might succeed in capturing the interest of students and enhance their satisfaction with the learning process.

MATERIALS AND METHODS

The study was carried out in Foundation University Medical College, Rawalpindi (Pakistan) on first year medical students of the year 2010 (n= 87). Institutional review waved off the requirement of ethical approval. The students were given handouts of the case study/Story adapted from: “The case of the dividing cell: mitosis and meiosis in the cellular court” (http://www.sciencecases.org/mitosis_meiosis/mitosis_meiosis.asp) by Clyde Freeman Herreid. Copyright held by National center for case study teaching in science, University at Buffalo, state university of New York. Used with permission ^{6,7}. The students were advised to read the story before hand, so that they could do some pre-session preparation. During the learning sessions the students were divided into small groups of 25, each headed by a junior faculty member. They read out part of the story and sorted out what they already knew at this point and what were the learning issues which they needed to find out. Points of confusions were cleared by discussions among the students and the faculty members. The case was discussed in three interactive sessions, each lasting two and a half hours. The students were exposed to two triggers during the first two sessions followed by a wrap up session in which the faculty summarized the learning issues.

This case focused on the process of cell division (mitosis, meiosis) and gametogenesis, along with a little introduction of mutations. The case had an unusual format, with the cell organelles talking to each other and arguing in a clear voice. The setting of this case was in an imaginary court room in which the jury was made of Eukaryotic cells and the defendant was an oocyte who was charged of a mutation. The prosecution

and the defense called witnesses which included Mr. Spermatocyte and Mr. Nuclear membrane and so the testimony continued revealing the secrets of cell division (mitosis, meiosis) gametogenesis and mutations:

“.....The judge adjusted his plasma membrane over his shoulders and began speaking with a voice that seemed to resonate from the bowels of his endoplasmic reticulum. Let us see now. This is the case of the State vs. Egg Cell Number 6624223. This presents an unusual situation involving an alleged capital offence. The defendant is charged with being an undesirable mutant in the body politic. The penalty is death!.....”^{6,7}

At the end of the last session, the students were made to attempt a surprise assessment test which comprised of six multiple choice questions (one best type) and fill in the blanks type of statements. Moreover, they were given a feedback questionnaire consisting of 12 questions that students had to answer on an open scale of 1-10 (1 being the minimum score and 10 maximum) regarding the effectiveness of the case method as a tool for teaching anatomy. Open ended comments were also invited, in which the students were asked to reflect upon the learning experience. Both, the assessment test and questionnaire were anonymous. The data collected from the questionnaire and the results of the assessment was analyzed by SPSS.

RESULTS

The analysis of the evaluation form reflected the students opinion that the story induced critical thinking and reasoning (mean evaluation score of $6.19/10 \pm 2.63$). Most of the students felt that they enjoyed the sessions and would like similar sessions in future (mean evaluation score: $5.92/10 \pm 3.15$). Moreover, 83.8% of the students thought that the objectives of the session were amicably achieved (that is, their evaluation score was greater than 5/10). An overall satisfaction score of 6.52 ± 1.75 was obtained.

The mean of the result of the assessment test was 92.7 ± 10.4 % (Table 1).

The open ended comments generally confirmed that the students enjoyed the sessions, however, they felt that this methodology was more time consuming and less effective as compared to other modes of teaching. Some of the interesting comments are being quoted:

“The session was captivating, less tiresome and it was fun to learn” Student

“The case was fascinating and evoked active learning, but at the same time it conveyed less information as compared to traditional lectures by senior faculty members.” Student

“The story captured more interest as compared to standard teaching methods and helped to facilitate the learning of Anatomy, yet it was more time consuming and probably this method cannot be used for teaching all aspects of anatomy” Student

“I feel that although the case was creative, but it was probably more suitable for high school students rather than professional students of the medical school. The cases or stories used for medical students should have a clinical setting.” Student

Open ended comments were also invited from the faculty members involved in the session. They all unanimously gave approximately the same comments, and according to one of them:

“The case method captivated the student interest, encouraged critical thinking and group activity. However, longer sessions were required and some of the objectives were not achieved naturally. The methodology should only contribute to a part of the anatomy curriculum and more traditional methods of teaching anatomy should be continued.”

Faculty member

Table 1: Evaluation of the Storytelling Method as a Teaching Tool

Evaluation score: 1 to 10 (minimum score is 01 & maximum score is 10)

S#	Criteria for Evaluation	Score Mean \pm SD
1	Were the objectives of the session clear?	7.05 \pm 2.29
2	Were the objectives met after the session?	6.71 \pm 2.47
3	Did the session facilitate active learning?	6.89 \pm 2.52
4	Was the problem structured in a way that naturally leads to the learning objectives?	5.89 \pm 2.74
5	Did the session improve critical thinking and reasoning?	6.19 \pm 2.63
6	Would you like similar sessions in future?	5.93 \pm 3.15
7	How do you compare such sessions with PBL sessions as regards to learning?	6.29 \pm 2.34
8	How do you compare such sessions with large group interactive sessions?	6.63 \pm 2.60
9	Was the physical environment (seating arrangement, noise and room temperature etc.)?	6.46 \pm 2.69
10	Was the working atmosphere (attitude and behavior of faculty inductive for learning process?	7.57 \pm 2.28

DISCUSSION

Anatomy is one of the most important subjects taught in the pre clinical medical years⁸, and the importance of teaching this subject beyond the initial years of medical school all the way upto postgraduate medical training is gaining importance⁹. At the same time, the faculty of Pakistani medical schools is showing an increasing concern regarding stress in their students. According to a study, 50% of medical students complain of stress due to increased cognitive load¹⁰. Therefore, efforts are being made to decrease the stress on the students and to make the curriculum more palatable for them by introducing different more interesting teaching methodologies. In the present study, storytelling has been used as a teaching tool. The story used has a message and is not simply a narrative for entertainment; its purpose is to achieve the learning objectives in an interesting manner. The present study showed an overall increase in student satisfaction and interest on using story as a means of learning. Similar results were obtained in another study where teaching of dental anatomy to dental school students was positively affected by storytelling and their satisfaction was compared with a control group which was exposed to traditional teaching methods¹¹.

According to a study, when “cases” were used for teaching the students of nursing, it improved their learning and engaged them in critical thinking and active learning¹². Another benefit of using storytelling highlighted by the present study was that this methodology encouraged positive group dynamics and facilitated learning through active help and support from their own class fellows. Previous studies have proved that active learning in groups has well established benefits with positive effects on assessment scores, skill development and student satisfaction¹³.

At the same time, medical educators are facing the difficult dilemma of decreased time available for teaching as a result of increased demands for clinical time¹⁴. The results of the present study indicate that both the students and the involved faculty felt that although the storytelling method of teaching encouraged critical thinking it consumed more time to achieve the same objectives as compared to traditional lectures, and that not all aspects of anatomy could be taught through this method. This is in accordance with studies which declare that that most of the aspects of basic sciences (especially anatomy) are not covered adequately by using cases⁸.

Moreover, results of surveys reveal that 75 % of the students are interested in short, specialized dissection sessions even during the clinical part of their training¹⁵. Therefore, cadaver dissection sessions should be considered as an integral part of anatomy curriculum in preclinical and clinical studies.

Keeping the above discussion in mind, it is recommended that a hybridized approach should be used for teaching anatomy. The important topics which are not covered through stories can be taught in lectures, dissection sessions or tutorials. It is also felt that the implementation of storytelling as a tool for teaching anatomy should be associated by a close follow-up of each student with regular feedbacks on his work, and integration of different teaching methodologies as and when required.

Further studies are however, necessary to compare the long term knowledge level of medical students who learned anatomy through newer modes of teaching versus traditional methodologies¹⁶. Presently, the evidence regarding the learning of Anatomy by storytelling is scant, but it is hoped that with this initiative, further opportunities will arise to gather such evidence. It is also anticipated that this paper will contribute to an ongoing debate, regarding the newly introduced teaching methodologies for anatomy on long term basis.

CONCLUSION

Results of the present study indicate that learning anatomy by storytelling captures the interest of majority of the students who find it an effective and captivating teaching methodology. However, other traditional tools of teaching should also be an integral part of the learning/ teaching of anatomy.

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Address for Corresponding Author:

Dr Huma Musarrat Khan
House No. 172, Street 61, Sector I-8/3,
Islamabad - Pakistan.
Postal Code: 44000
Phone: 051-4444232. Cell: 0333-5115551
Email: huma.anat@gmail.com

Original Article

Clinical Spectrum of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

1. Abdul Kareem Zarkoon 2. M. Saleem Khan Barrech 3. Zahir Khan Mandokhail
4. Azimullah Asif Jah Gorya

1. Assoc. Prof. of Nephrology 2. Assoc. Prof. of Neurology 3. Assoc. Prof. of Neurology 4. Incharge PMRC,
Bolan Medical College Quetta.

ABSTRACT

Objective: To evaluate the clinical spectrum of autosomal dominant polycystic kidney disease (ADPKD).

Design of study: Hospital base perspective and retrospective study.

Place and duration of study: This study was conducted in Department of Nephrology Sandeman, Provincial Hospital Quetta, from Nov. 2008 to Dec. 2010.

Patients and Methods: In this study, 50 patients were taken with autosomal dominant polycystic kidney disease diagnosed by abdominal ultrasonography which were evaluated for their clinical spectrum by symptoms, clinical examination, ultrasonography, urine detailed report, urea, creatinine, 24 hours urinary creatinine and also evaluate for the extra-renal manifestation by abdominal ultrasonography, gastrointestinal endoscopy and computed tomography (C.T Scan) of brain.

Key Words: Polycystic kidney, hypertension, haematuria, UTI, flank pain, hepatic cyst, diverticular disease

INTRODUCTION

Autosomal dominant polycystic kidney disease is defined genetically by its dominant inheritance and pathologically by cystic dilatation of nephrons. ADPKD is world wide distribution, its exact incidence in Pakistan is not known but seen quite frequently. Most of the cases of ADPKD became clinically apparent after the age of 40 years but may present at the age of 8-80 years. The diagnosis of the ADPKD is usually made during evaluation of the patient for abdominal pain or flank pain, haematuria or hypertension. Less frequent patient may present with sign and symptoms of urinary tract infection or renal insufficiency or aware of abdominal mass or during investigation because of a strong family history. The most frequented highly sensitive method for diagnosing of ADPKD is abdominal ultrasonography which shows bilaterally enlarged kidneys with multiple contiguous cyst of various sizes in the cortex medulla. However computed tomography (C.T Scan) and Magnetic Resonance Imaging (MRI) can be used. The system effected in ADPKD include, besides kidneys are gastrointestinal tract in which hepatic cysts and diverticular disease are most common. In cardiovascular system mitral valve prolapsed and intracranial aneurysm in brain is most common.

MATERIALS AND METHODS

This study includes 50 Cases of ADPKD. Diagnosis of ADPKD was established on detailed history, physical examination and ultrasonography. All 50 patients entered into the study were diagnosed ADPKD, documented by ultrasonography studies as defined by

the presence of at least four renal cortical cyst bilaterally¹.

The Diagnosis of ESRF in ADPKD was made on the basis of:

1. Bilateral renal cortical cysts leading to distortion of renal parenchyma on Ultrasound.
2. Creatinine clearance less than 10ml/mint.
3. Serum creatinine more than 10 mg/dl.
4. Gradual progression of renal failure.

5. Exclusion of other conditions causing acute on chronic renal Impairment e.g., sepsis, uncontrolled hypertension, volume depletion and drug induced There was no exclusion criteria. Other initial laboratory workup included complete blood picture, serum urea, creatinine level, serum electrolytes, routine urine examination and liver function test, urine C/S. ECG, Echocardiography and in suspected cases investigate through barium meal to rule out diverticular disease. C.T. Scan of the brain was also done in a patient with a family history of CVA. All the cases were assessed by neurologist. The findings of history, physical examination, extra-renal manifestation and other related laboratory work up were recorded on a comprehensive Performa especially designed for this study. Majority of the patients were followed up for up to more than six month. 28 patients are still visiting our OPD. 10 patients were kept on maintenance HD during 2 years period. Four of them died because of other complications related to ESRD. transplant was not done in any patient because of restricted hospital policy, only for live related donor.

RESULTS

In our study 50 cases of ADPKD were entered. They were between 30-70 years of age with a mean age of 44 years. 32 were Male and 18 were female. Majority of ADPKD patients 38 (76%) were having Impaired renal function and of which 21 (42%) has reached end Stage renal failure and remaining 17 (34%) patients were having chronic renal failure but not reached the ESRD. 12 patients (24%) were having normal function. Two Commonest clinical findings were flank pain in 22 cases (44%), Gross haematuria was present in 11 cases (22%) and microscopic haematuria was present in 17 cases (34%) so the overall case of haematuria were 28 (56%). urinary tract infection were found in 12 cases (24%). The most common clinical finding was hypertension and in 35 cases (70%). Palpable flank masses were found in 13 cases (26%). Polycythemia was noted in 6 cases (12%).

Renal calculi were detected in 16 cases (32%). Hepatic cyst was the commonest extra-renal manifestation of ADPKD and were found in 19 cases (38%). Intestine diverticular were detected in 11 cases (22%) and mitral valve prolapsed in 10 cases (20%).

DISCUSSION

ADPKD is a disorder characterized by remarkable cysts formation with in the Kidney. It is one of the most common human genetic diseases². It is estimated that about 8-10 % of the patients in the dialysis population belongs to ADPKD³. In this study total 50 cases of ADPKD were studied for their clinical spectrum and has been observed that the disease is more common in male (32 cases) as compared to females (18 cases) where according to previous report.⁴ There is no sex differentiation. It is not known the exact explanation of the higher incidence of ADPKD in males our study but it is probably related to the fact that our society is male dominated and opportunities to seek medical advice as compared to female. In onset of disease, presentation is almost parallel to the previous studies done regarding the age. It has been observed that majority of patient (42) out of total 50 cases were between the age of 40 – 70 years with the maximum numbers (24) who presented with the disease in the 4th decade. In our study we were only able to get strong evidence of family history of ADPKD in 18 cases (36%). We were not able to find familial history of ADPKD in 32 (64%) cases after through interrogation with their families. These are quite significant numbers and explain the fact that most of the families do not know the cause of death of their immediate ancestors. In the western literature the incidence of positive family history is about more than 60%.⁵ Another important factor regarding the higher incidence of positive family history of ADPKD in western society is related to the better health care

delivery system to the common people. Whereas in the developing countries like Pakistan, the health care system is very poor and there is no facility of screening of the families with such a common genetic disease. In our study 21 cases (42%) had end stage renal disease (ESRD) while 17 cases (34%) showed impaired renal function manageable by conservative treatment. Out of 50 ADPKD patients only 12 cases (24%) were of normal renal functions manageable by conservative treatment. The number of ESRF patient in our study is higher as compared to 25%.⁵ This possibly due to delayed diagnosis and delay in seeking medical advice. For the purpose of description of all 50 patients are divided into two groups according to the age of patient at the time of presentation. There were 32 patients who are less than 50 years age, only 9 patients (28%) presented with ESRF. In second group, there were 19 patients with more than 50 years of age, 12 cases (67%) having ESRF. We also observed nearly the same incidence of CRF (manageable conservatively) age wise. These result showed that increased age is major risk factor for ESRF in ADPKD⁵. The incidence of ESRF is 50% between 50 and 60 years of age and 75% by the age of 70 years. Flank pain was the commonest presenting symptom of ADPKD in our study. It was present in 22 cases (44%) for which they came to the hospital to see medical advice. There are conflicting reports regarding the commonest presentation of ADPKD in the western literature. In a study showed the incidence of flank pain in 30% while it is 50-60% as reported^{6,7}. The second most common presentation of ADPKD was urinary Tract Infection (UTI) and it is seen in 12 cases (24%) in the study. A study reported 19% incidence of UTI in ADPKD⁶. Gross haematuria was the third commonest presenting feature in ADPKD patients in the study. It was the presenting feature in 11 cases (22%). A study reported 15-20% incidence of gross haematuria⁷. Hypertension is commonest occurrence in ADPKD patients. It is noticed in 35 cases (70%). There were 17 cases with impaired renal function but not reached the ESRF out of which 18 (85%) were having hypertension. There were 17 cases with impaired renal function but not reached the ESRF, 12 (70%) have had hypertension where as there were 12 cases with normal renal function out of which 5 (41%) were found hypertensive. 50-70% incidence of hypertension that occurs in early course of ADPKD⁸. Cyst enlargement causing bilateral renal ischemia and subsequent release of rennin is proposed in this study is the cause of hypertension in ADPKD patients. Our present results of hypertensive population in ADPKD patient also show nearly parallel incidence of hypertension as in above mentioned studies^{9, 10, 11}. In our study it also appears that hypertension is an early event in natural history of ADPKD. Renal calculi has been reported in 16 (32%) cases associated with ADPKD. In a study, reported renal calculi in 34% of

the cases⁶. Palpable renal masses were found at the time of presentation in 13(26%) in our study. It is higher as compared to previous studies by Delaney in which he reported palpable renal masses in 15% of the cases. The higher incidence in our study is possibly due to delay in the referral of the patients, as the most of the patients were presented in very advanced renal disease. Polycythemia was associated with ADPKD in 6(12%) in our study. It is observed in non-azotemic patients on dialysis than other dialyzed patients, reflecting the presence of higher level of erythropoietin. Hepatic cysts were found to be associated with ADPKD in total 19(38%) cases out of which 13(26%) patients who were having hepatic cyst (2 patients also had pancreatic cyst) were more than 50 years age, being extremely uncommon before the age of 30 years. Although there were sizeable structure involvement of the liver, did not show abnormal liver function test. According to a study, the increase incidence of hepatic cysts with the increasing age⁷. The principle non-cystic gastrointestinal manifestation in our study was colonic diverticular. It is reported in 11(22%) of cases. None of the patients in our study had colonic Perforation, although it has been reported in few cases¹². In the western literature incidence of diverticular disease in ADPKD patients is reported 83% of patient on hemodialysis. The lower incidence in our study is due to the fact that we had performed barium studies only selected symptomatic cases. Mitral valve prolapsed (MVP) was found to be associated in 10 cases(20%) in our study, which near to the prospective studies¹³ in which they reported 26% frequency of MVP in ADPKD, as compared with frequency of 20% in control population, palpitation and non-exertional chest pain were the main symptoms in our patients of mitral valve prolapsed. One of the most devastating extra-renal manifestation is intra-cranial secular aneurysm (ICA), which has not been observed in our study. The reason of not finding ICA is that we have not performed C.T or MRI in all our cases studied. The exact frequency of ICA varies from (0-41%)¹⁴. There is three recent American prospective studies, one found no aneurysm in 96 patient on either C.T Scan or MRI studies¹⁰. The second found aneurysms in 4 of 92 patients, 3 of whom had multiple aneurysms. This study use C.T scan with 2mm cuts in the axial and coronal planes, angiography, or both¹⁶. The third study used magnetic resonance angiography and detected aneurysms in 9 of 85 asymptomatic patients with ADPKD¹⁷.

CONCLUSION

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the one of the common hereditary disorders. Our experience in this study confirmed that the ADPKD is one of the important causes of ESRD in

our country. The most common findings were hypertension, flank pain and hematuria. Large number of patient with ADPKD presented with end stage renal failure which reflects a delay in diagnosing this disease. About half of our total patients at the time of presentation were more than 40 years of age. We have also observed a higher incidence in males. In one third of the cases there was a strong evidence of family history, while remaining two third of the patients were not able to document family history of ADPKD. The most common extra-renal manifestation were hepatic cysts, colonic diverticular and Mitral Valve Prolapse in decreasing order. There is no published local data available regarding this common hereditary disorder to help us to compare the clinical spectrum of this disorder. In this study we have observed that Ultrasonography is a valuable diagnostic tool ADPKD and that a relationship exists between structural and function abnormalities suggesting a pathogenic role of cysts in the development of signs and symptoms. These observations provide important counseling information for physicians caring for these patients, and they enable investigators to develop criteria upon which to base future interventional studies.

RECOMMENDATIONS

On the basis of our experience in ADPKD, our recommendation for patients with this disease are:

1. Blood pressure should be closely and regularly monitored and it should be maintained as normal as possible.
2. Yearly renal function test in non-azotemic patients and quarterly in Azotemic patients.
3. UTI should be treated with appropriate antibiotics.
4. Instrumentation of urinary tract should be avoided.
5. For hematuria bed rest, hydration and pain control will improve the symptom within a week.
6. Avoid strenuous physical exercise or trauma.
7. Screening of family members.
8. Counseling for family planning.

The risk of transfer of ADPKD gene to fetus should be explained to the parents. If the facilities of gene linkage techniques are available then either amniocentesis chronic villous sampling can be used for DNA analysis. In fetus is found with defect gene then the parents should be informed and the choice to terminate the pregnancy should be discussed or another option although practically difficult in our society would be to avoid conception and to consider an adopted child.

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Address for Corresponding Author:

Abdul Kareem Zarkoon,
Assoc. Prof. of Nephrology,
Bolan Medical College Quetta.

Seminar Report**Quacks behind Deafness and other Diseases****Mohsin Masud Jan****Editor**

Medical experts have emphasised the need to create awareness among people about not going to quacks as they are a major source of spreading diseases, including deafness, in people on mass scale.

“The government must take stringent action against roadside quacks, who are spreading innumerable diseases, including deafness, among the unsuspecting people,” they said while speaking at a seminar on “21st Century - Deafness is no more an issue” organised by the Mir Khalil-ur-Rahman Memorial Society (Jang Group of Newspapers) in collaboration with the Deafness Foundation of Pakistan here at a local hotel the other day.

Speaking on the occasion, Deafness Foundation of Pakistan Chairman and ENT specialist Dr Nasrullah Rana said people should neither visit quacks nor resort to self-medication specially in case of hearing loss and he advised them to only go to qualified consultants for their treatment in this regard.

He also pointed out that people had mistaken ear wax as ear filth and tried to remove it through various means, which might cause deafness, adding that ear wax was actually guard against deafness and prevents hearing loss. “Cotton bud, match-stick, hair-pin and keys should not be used to clean ears,” he advised people and prohibited them from putting oil in ears as well. He also advised people not to slap on the face of children as it could also cause deafness.

He also suggested that the people with hearing disability should accept hearing aid, as people with weak eyesight accept glasses, to improve the quality of life and it should not be taken as a stigma. The hearing implant could also help compensate hearing impairment in children, he said.

In elderly age, he said, deafness and depression go side by side. He said proper treatment of deafness could also help prevent depression in old age. Justice (retd) Munir A Sheikh, former federal Ombudsman and honorary patron-in-chief of Deafness Foundation of Pakistan, said the Deafness Foundation of Pakistan had waged a struggle against deafness and working on the slogan “Hearing for All” by providing useful information to the masses for prevention of deafness. He said deafness was increasing due to careless attitude of the people. He also lamented that society segregated people with deafness and called upon the people not to adopt discriminatory behaviour with the people with hearing impairment.

He stressed the need to spread awareness among the people to prevent deafness. Punjab Parliamentary Secretary of Health Dr Saeed Elahi said health facilities/hospitals and medical expertise in Pakistan were far better than in neighbouring countries like India, Bangladesh and other countries across the border. He said there was no shortage of talent in the country however there was a need to streamline the talent and work hard with dedication.

Prof Dr Nazeefa Ahmad, head of the Department of Pathology at Fatima Jinnah Medical College, said that careless behaviour of the people was among various other reasons of deafness.

“The children are used to put several things in their ears, which bursts the membrane in ear, which causes deafness among children,” she said and added that the parents must take care of the activities of their children. She said hearing ability of the people staying in high-noise environment might also affect. Besides, she said, continuous use of Aspirin might also cause deafness. Similarly, the diabetics might also lose hearing ability. “The delay in timely treatment of ear infection can also cause hearing impairment,” she added.

Saima Kausar, chairperson of Mass Communication Department, said private TV channels should allocate specific time for highlighting health issues in addition to news and entertainment for the benefit of the masses. She also called upon the NGOs to work more in health sector.

She urged the government to establish special health centers and schools for deaf people for their proper rehabilitation, adding that the government should also allocate a special quota in jobs for deaf people.