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EDITORIAL

Changing Patterns of Anti-Microbial Resistance and Their Financial Impact on Patient Care

Abdul Bari Khan, Shahina Yasmin

As defined by World Health Organization (WHO), "Antimicrobial resistance (AMR) occurs when microorganisms such as bacteria, viruses, fungi and parasites change in ways that render the medications used to cure the infections they cause ineffective."¹

AMR is a very serious threat of present time to the human health security all over the world. It has been reported against almost every anti microbial discovered so far and in every country or community on the surface of the globe. The antibiotic resistance (ABR) shown by bacteria is more prevalent globally and specially in low and middle income countries resulting in devastating results. The WHO, in one of the latest reports has described that globally 3.6% of all new cases and 20.2 % of previously treated cases of Tuberculosis (TB) are estimated to have multi drug resistant TB (MDR-TB) and on the average 9.7% of these MDR-TB cases are found to be extensively drug resistant (XDR-TB). Great concern has been aroused by antibiotic resistance shown by particular bacteria against specific antibiotic groups like methicillin resistant *Staphylococcus aureus* (MRSA), the extended spectrum beta lactamase (ESBL) producing gram negative bacilli and cocci leading to resistance against fluoroquinolones and 3rd generation cephalosporins, carbapenemase producing members of bacterial family enterobacteriaceae becoming resistant to almost all antibiotics including carbapenems, the last resort antibiotics for these and NDM-1 producing bacteria resistant to most antibiotics except Polymyxin. The other emerging threatening pathogens include 3rd generation cephalosporin resistant *Neisseria gonorrhoeae*, Vancomycin resistant Enterococci and Staphylococci, multidrug resistant *Salmonellae* and *Haemophilus influenzae*.²

About 10-17% of all new patients of HIV infection in

Australia, Europe Japan and USA are infected by virus resistant to at least one antiretroviral drug. Emergence of *plasmodium falciparum* resistant to almost the last resort antimalarial named Artemisinin is another dreadful threat. Similarly antimicrobial resistance against antivirals like adamantanes by influenza virus type A, and against anti-fungals like fluconazoles by *Candida* is among all types of antimicrobial resistances.²

Out of the above mentioned list, almost every type of antimicrobial resistance is present in Pakistan. But the most devastating and alarming are MDR and XDR *Mycobacterium tuberculosis*, Chloroquin and multi resistant plasmodia, ESBL and carbapenemase producing enterobacteriaceae, MRSA, Vancomycin resistant Enterococci and Staphylococci and multidrug resistant typhoid salmonellae.^{3,4,5,6}

Although sufficient numbers of comprehensive studies covering all aspects of the additional financial burden faced with infections by multi-resistant microbes are not found in medical literature, yet the longer hospital stay, increased hospital cost, and higher mortality have been reported in various studies.^{2,7} However it is confirmed that the increasing microbial resistance has got great economic impact on the patient care because 2nd and 3rd line regimens have been reported to be 3 times and 18 times more expensive respectively than the first-line drugs.⁸ More importantly, we are facing a global scenario where sporadic antimicrobial resistance has been found even to the last resort antimicrobials.⁹

In 2009 a joint technical report presented a data of financial impact of infections with multi resistant bacteria and reported death of 25 thousand patients who died in a year from infection by multi resistant bacteria in European Union (EU), Iceland, & Norway. In addition there were approximately 2.5 million extra hospital days due to infection by these organisms. The estimated financial burden both direct and indirect due to antibiotic resistant bacteria was found to be €1.5 billion (EURO) each year in EU.¹⁰ Centre for disease control and prevention (CDC) USA has cited a study of 2009 showing an estimate of as high as \$20 billion in excess as direct healthcare costs, and additional cost to society for lost productivity as high as \$35 billion a year in USA as a result of infections by multi resistant

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bacteria.¹¹ A recent study chaired by an economist have estimated that if the ever increasing bacterial resistance is not checked at this stage there would be 300 million deaths prematurely in the next 35 years leading to economic loss of 60 to 100 trillion USD by the year 2050.¹²

Pakistan is one of the top 10 countries in the world with high burden of tuberculosis. With an average of 510,000 new cases of tuberculosis including 26,000 cases of MDR TB and about 2,500 estimated cases of XDR TB puts a huge economic burden for its management and treatment in view of the estimated per person treatment cost for TB ranges from 100 to 1,000 US dollars in susceptible infection and 2,000 to 20,000 dollars for MDR TB. Moreover the success rate of TB treatment is up to 83% in susceptible patients, 52% for MDR TB and 28% for XDR TB.¹³ This shows that a very comprehensive infrastructure and huge funds other than current international donations are required to cope with the situation.

Similarly addition of 1.5 million cases of malaria every year with about 12% of these caused by *Plasmodium falciparum* and rest by *P. vivax* is a big figure for consideration. The current eruption of Chloroquin resistance in *P. vivax* can lead to a huge burden on health care budget of the country.⁶

A research report showing the total costs per malaria episode (including direct and indirect household costs and health system costs) based on disease severity and the presence of complications and co-morbidities ranged from US\$ 7.99 to \$ 229.24 in Ghana, from US\$ 5.2 to \$ 137.74 in Tanzania, and from US\$ 11.24 to \$ 287.81 in Kenya.¹⁴

Due to non availability of a comprehensive data the financial burden due to infections by MRSA, ESBL and carbapenemase producing organisms for our country is difficult to calculate. We have compared the cost of the antibiotics only for 10 days treatment of a patient suffering from some systemic disease caused by *Escherichia coli* sensitive to 3rd generation cephalosporins and resistant to that and treated with meropenem. The cost of antibiotics comes to Rs 7,500 -15,000 and 30,000 -60,000 respectively. This example can show us how multi resistant organisms can influence the health care budget of a hospital, family and a country.¹⁵

In view of above, there is an utmost requirement of having serious considerations is planning and execution of preventive measures against rapid development & spread of AMR at individual, hospital, community, national and international level.

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ORIGINAL ARTICLE

Causative Organisms and Their Sensitivity Pattern of Urinary Tract Infection in Children

Sidra Tul Muntaha,¹ Mutassim Ismail,² Farhan Hassan³

ABSTRACT

Objective: The objective of this study was to determine the frequency of pathogens and their drug sensitivity pattern in children presenting with urinary tract infections.

Study Design: It was a cross sectional study.

Place and Duration of Study: The study was conducted in 6 months from Nov 01, 2013 to Apr 30, 2014 at casualty and outpatient departments of Pediatrics at Benazir Bhutto Hospital, Rawalpindi.

Materials and Methods: All the children between 1-12 years of age with one or more symptoms of UTI were included in study. The collected urine samples of the patients were transported immediately to the laboratory for urinalysis, culture and sensitivity. Cultures were done directly on CLED agar medium and incubated for 48 hours at 37°C. Sensitivities were checked for Trimethoprim-Sulfamethoxazole, Amoxycillin-Clavulanic acid, Nalidixic acid and others. All data were entered and analyzed in SPSS version 16.

Results: Out of 155 children, 72.26% (n=112) had E.Coli, 14.84% (n=23) had Klebsiella Pneumoniae, 10.32% (n=16) had Staphylococcus Saprophyticus and 2.58% (n=4) had others. These bacterial pathogens were sensitive to Amoxycillin-Clavulanic acid and Trimethoprim-Sulfamethoxazole.

Conclusion: The results of the study revealed that Escherichia coli followed by Klebsiella and Staphylococcus saprophyticus are the leading pathogens of urinary tract infection in children. Out of three antimicrobials studied, Amoxycillin-Clavulanic acid and Trimethoprim-Sulfamethoxazole have been found to be superior in efficacy as compared to Nalidixic acid.

Key Words: Urinary Tract Infection, Children, Pathogens, Sensitivity.

Introduction

The term Urinary tract infection (UTI) indicates the invasion by microorganisms of previously sterile urinary system. The worldwide incidence of urinary tract infection in children is 30%.¹ In USA the incidence of UTI in children is 3-7% in girls and 1-2% in boys.² The prevalence ranges from 2-8% throughout childhood.³ However, in Iran the incidence of UTI is comparatively lower than the western world about 3% of girls and 1% of boys experience first episode before reaching 11 years of age.¹ Childhood UTI requires early diagnosis as it

causes renal damage by renal scarring leading to end stage renal disease.⁴

Increasing resistance of bacterial pathogens is of worldwide concern that is varied in different regions and even countries.⁵ Most UTIs in developing countries are treated on an empirical basis; thus treatment should be based on available local data regarding the susceptibility of common pathogens to antibiotics.⁶

There is increase of antibiotic-resistant strains, which are created because of antibiotic abuse and inappropriate choice of antibiotics; however the recent development of new antibiotics has led to changes in the antibiotic susceptibilities of the pathogens.⁷

Different studies have shown study that the most commonly isolated organisms from urine culture were Escherichia Coli (66.3%), Staphylococcus Saprophyticus (14.9%), Klebsiella Pneumoniae (11%) and the highly active antibiotic against them was Nalidixic acid (70%), and then Amoxicillin-Clavulanic acid (29.9%), Co-trimoxazole (16.4%).^{1,8}

This study was designed to determine the microorganisms and the sensitivity patterns of these organisms to various drugs. The result of the study

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would provide future guidelines for effective prescribing practices and management of UTIs for our population. The exact information about the infecting organism and pediatric UTIs in a region is usually not available, and if available it is outdated as antimicrobial sensitivity patterns are bound to change over a period of time. This study aims to facilitate the empiric treatment of patients with symptoms of UTIs. Moreover, the data would also help authorities to formulate antibiotic prescription policies, at least for a region.

Materials and Methods

This was cross sectional descriptive study. Duration of the study was six months from Nov 01, 2013 to Apr 30, 2014 and sampling technique was non-probability purposive. All children between 1-12 years of age of either sex presented with one or more clinical symptoms of UTI were included. All children who have already taken antibiotics in the past 24 hours, already catheterized, uncircumcised males or children with phimosis or paraphimosis were not included in study. Basic demographic information including name, age, gender, weight, and height was collected. Midstream urine samples of 155 patients were collected by aseptic measures for routine examination and culture sensitivity in children older than 2 years, by sterile adhesive pediatric urine bag in children up to 2 years and by suprapubic aspiration in children between 1 to 2 years of age, if necessary. The collected samples were transported immediately to the laboratory for urinalysis and culture and sensitivity. UTI was defined by the presence of a pure growth of more than 10⁵ colony forming units of bacteria per milliliter of urine. Cultures were done directly on CLED agar medium for 48 hours. Antibiotics sensitivity was tested using disc diffusion technique by using various antibiotic discs as per guidelines of national committee for clinical laboratory standards.⁹ Sensitivities were checked for Trimethoprim-Sulfamethoxazole, Amoxycillin-Clavulanic acid, Nalidixic acid and others. Urine culture and sensitivity reports were evaluated and isolated microorganisms along with their sensitivities to the mentioned drugs were entered in already designed Performa and all the reports were verified by the Pathologist. All data were entered and analyzed by SPSS version 16. Mean and standard deviation were calculated for age,

weight and height. Percentages and frequencies were calculated for gender, commonly isolated microorganisms (*Escherichia Coli*, *Klebsiella Pneumoniae* and *Staphylococcus Saprophyticus*) and their sensitivity patterns to various drugs (Trimethoprim-Sulfamethoxazole, Amoxycillin-Clavulanic acid, Nalidixic acid and others).

Results

Age distribution of the patients showed that 56.13% (n=87) were between 1-6 years of age and 43.87% (n=68) were between 7-12 years of age, mean +SD was calculated as 7.54+2.61 years. According to gender, 36.77% (n=57) children were males and 63.23% (n=98) were females. Mean weight and height of the patients were recorded which came out to be 24.48+7.29 Kg and 110.29+35.21 cm respectively.

Frequency of pathogens in children with UTI was recorded as shown in Table I. Sensitivity pattern of various drugs for pathogens was recorded which showed *Escherichia Coli* (E. Coli) most sensitive to Trimethoprim-Sulfamethoxazole (66%), *Klebsiella Pneumoniae* to Amoxycillin-Clavulanic acid (74%), and *Staphylococcus Saprophyticus* to Amoxycillin-Clavulanic acid (76%) as shown in Table II.

Table I: Frequency of Pathogens in Children with UTI (n=155)

Pathogens	No. of patients	%
<i>Escherichia Coli</i>	112	72.26
<i>Klebsiella Pneumoniae</i>	23	14.84
<i>Staphylococcus Saprophyticus</i>	16	10.32
Others	4	2.58
Total	155	100

Table II: Frequency of Sensitivity Pattern of Various Drugs for Pathogens in Children with UTI (n=155)

Pathogens	Sensitivity
<i>Escherichia Coli</i>	Trimethoprim-Sulfamethoxazole (66%) Amoxycillin-Clavulanic acid (62%) Nalidixic acid (51%) Others (18%)
<i>Klebsiella Pneumoniae</i>	Trimethoprim-Sulfamethoxazole (58%) Amoxycillin-Clavulanic acid (74%) Nalidixic acid (46%) Others (11%)
<i>Staphylococcus Saprophyticus</i>	Trimethoprim-Sulfamethoxazole (73%) Amoxycillin-Clavulanic acid (76%) Nalidixic acid (48%) Others (16%)

Discussion

In this study, out of 155 children, 36.77% (n=57) were male and 63.23% (n=98) were females with female to male ratio of 2.5:1.4. Yolbas I et al. in their study analyzed age and gender-wise data of the prevalence of uropathogens in community-acquired urinary infections. They found that all the organisms were more common in females than males with ratio of 3.9:1.1 which is in agreement with our study.¹ Data from other international studies on pediatric patients also report that UTIs are more common in females, which is similar to our finding.^{10,11} However unlike our study, Kalantar et al. in his prospective study of 1696 children aged up to 5 years reported male to female ratio of 1.07:1.¹² Jahanzeb et al. in their study included children up to 12 years of age and found that UTI is more common in males with an overall male to female ratio of 1.2:1.¹³ During the first year of life males were infected more than females. This was also reported by all other researchers, observed as 2.8-5.4:1.0 in the first year of life and changing to 1:10 in the second year of life because in infancy more common in uncircumcised males and later in life more common in females due to shorter length of urethra in females which shortens the distance of travel for bacteria to reach the urinary bladder.¹⁴

Frequency of pathogens in children with UTI was recorded, it showed that 72.26% (n=112) had *E. Coli*, 14.84% (n=23) had *Klebsiella Pneumoniae*, 10.32% (n=16) had *Staphylococcus Saprophyticus* and 2.58% (n=4) had others. *E. coli* (72.26%) was the leading infecting organism of pediatric UTI at our center. This is in consistent with studies reported by Mashouf et al.¹⁵ (57.4%) in Iran, Kalantar et al.¹² (54.8%) in Iran, Brad et al.¹⁶ (58%) in Romania. Data from the above studies showed that *E. coli* are consistently found predominant uropathogen irrespective of country, community or hospital setting. Our study demonstrated *Klebsiella Pneumoniae* in 10.32% subjects. Yolbas I et al. in a study, showed similar data with *Klebsiella* spp. being detected in 20.7%¹ cases and in various parts of the world as 14.0%,¹¹ 14.5%¹⁴ and 21.0%¹³ cases. Findings of study is in agreement with another study showing the most commonly isolated organisms from urine culture were *Escherichia Coli* (66.3%), *Staphylococcus Saprophyticus* (14.9%), *Klebsiella Pneumoniae* (11%)

and the highly active antibiotic against them was Nalidixic acid (70%), and then Amoxicillin-Clavulanic acid (29.9%), Co-trimoxazole (16.4%).^{1,9} In a study conducted by Nayek K et al, author indicated a lower percentage of *E. Coli* infections and a higher infection with *Proteus* and *Klebsiella* species. This could be explained on the basis of sampling technique and the different proportion of males to females in different studies.^{17,18} On the other hand some have given a higher percentage of *E. Coli* infection as compared to other organisms which is in agreement with our study.^{19,20}

We found a valuable laboratory data on antibiotic susceptibilities of uropathogens which allows comparison of the situation in our area with that in other countries and other regions of our country. Amoxycillin-Clavulanic acid and Trimethoprim-Sulfamethoxazole were the most sensitive antibiotics in our study. These results are in agreement with many other published articles.^{21,22}

A study in Turkey by Rodríguez-Baño J et al. also reported that with Amoxicillin-Clavulanate, cure rate of patients with cystitis was 93%, cure rates were 93% in children with susceptible isolates (MIC < or = 8 µ/mL).²³ A study by Çoban B et al showed sensitivity to trimethoprim-sulfamethoxazole (56.9%), and to amoxycillin-clavulanate (65.2%). They followed up patients for period of 5 years and observed the resistance of *E. coli* to amoxycillin-clavulanate decreased from 40.3% to 31.3%, while the resistance to trimethoprim-sulfamethoxazole decreased from 45.6% to 34.7%.²⁴ A study by Jackowska T et al. showed, 86% cases of urinary infection were caused by one of the isolated pathogens i.e. *Escherichia coli*, *Klebsiella pneumoniae* or *Proteus mirabilis*. *Escherichia coli* was the most common isolated pathogen (70-74%). Frequency of isolating of *Klebsiella Pneumoniae* grew from 6 to 10%. Likewise, in the period of two years they observed the level of the susceptibility to trimethoprim-sulfamethoxazole (90-91%) remained same and a non-statistically significant lowering of susceptibility to aminopenicillins, and aminopenicillins combined with beta-lactamase inhibitors from 92 to 74% (p=0.2).²⁵

Another study by Mirsoleymani SR²⁶ concluded from 19,223 collected samples that predominant agents of UTI were successively *E. coli* (65.2%; 95%),

Klebsiella Pneumoniae (26%; 95%), Pseudomonas aeruginosa (3.6%; 95%), Staphylococcus coagulase positive (3.7%; 95%) and Enterobacter species (0.4%; 95%), and our findings are consistent regarding the most common pathogen of the morbidity.

Conclusion

Escherichia Coli followed by Klebsiella Pneumoniae and Staphylococcus Saprophyticus are the leading pathogens in children with UTI. Amoxycillin-Clavulanic acid and Trimethoprim-Sulfamethoxazole are superior in efficacy as compared to Nalidixic acid. Hence Amoxycillin-clavulanic acid or Trimethoprim-sulfamethoxazole can be used safely when urine culture reports are awaited.

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ORIGINAL ARTICLE

Decreased Cord Blood Albumin: A Predictor of Neonatal JaundiceErum Rashid Chaudhry¹, Abdul Khaliq Naveed², Amena Rahim³, Zunnera Rashid Chaudhry⁴**ABSTRACT****Objective:** To determine the significance of cord blood albumin estimation as a predictor of neonatal jaundice.**Study Design:** It was a prospective observational study.**Place and Duration of Study:** This study was carried out in Gynae/OBS department, neonatal intensive care unit and pathology laboratory at Railway Hospital Rawalpindi in collaboration with the Biochemistry Department of Islamic International Medical College from June 2015 to March 2016.**Materials and Methods:** Ninety full term neonates were divided into three groups based on their cord blood albumin concentration. Group I, with albumin less than 2.8 gm/dl, Group II with albumin between 2.8 - 3.3 gm/dl and Group III greater than 3.3 gm/dl. Serum Bilirubin level more than 1mg/dl was taken as standard for all the groups. Follow up was done for those neonates who had albumin less than 3 gm / dl and bilirubin more than 1 mg/dl. The babies were followed up on 7th and 15th day for the appearance of jaundice. Depending upon the extent, and delayed recovery from jaundice they were followed up to 20th post delivery day.**Results:** It was found that all neonates of group I and II who had albumin levels less than 3.3gm/dl, developed jaundice. Out of these 16.75% from group I received phototherapy and only 3% needed exchange transfusion. Whereas 10% jaundice neonates from group II received phototherapy. Out of 30 neonates in group III, 60% neonates developed jaundice but none required phototherapy or exchange transfusion.**Conclusion:** It is concluded that low albumin levels in the cord blood taken after birth is a good predictors of neonatal jaundice.**Key Words:** Albumin, Bilirubin, Cord Blood, Neonatal Jaundice, Predictor.**Introduction**

Neonatal jaundice is one of the most common conditions requiring medical attention in newborn babies. About 60% of neonates born at term and 80% of neonate born before term (preterm) develop jaundice in the first week of life.¹ It is also known as icterus neonatorum and in the first postnatal week, approximately two thirds of all newborns develops icterus neonatorum in which bilirubin deposition occurs in the skin and mucous membrane. In majority of neonates such deposition is of little consequence.² It is mostly physiological since liver is not mature enough to handle the bilirubin load and this increased load is due to a higher circulating erythrocyte volume, a shorter erythrocyte life span,

and a larger bilirubin peak.³ Bilirubin is a yellow colored pigment which is produced from hemoglobin during destruction of erythrocyte. So increased production, impaired uptake of bilirubin by liver and in-effective conjugation causes increase level of unconjugated bilirubin leading to hyperbilirubinemia.⁴ For the detection of potential severity of neonatal hyperbilirubinemia the main criterion is the serum concentration of free bilirubin, or if it cannot be determined, the bilirubin/albumin ratio is taken.⁵ Bilirubin is normally glucuronidated and excreted by the liver into bile. Failure of this system can lead to a buildup of conjugated bilirubin in the blood, resulting in jaundice.⁶ There are several neurotoxic effects attributed to jaundice like sensorineural deafness, neonatal seizures, auditory neuropathy, cerebral palsy and apnoea.⁷ It has been observed that during the first week of life unconjugated serum bilirubin level is more than 1 mg/dL (17 mol/L), in almost all neonates.⁸ Albumin is the major protein present in abundant amount in the blood and has the property of binding to many hormones and nutrients.⁹ Albumin has a specific site for binding with bilirubin and is responsible for transporting it to the liver, its flexible structure of the helps it to adapt readily to ligands, and it has three

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domain in its structure which offers a different kinds of binding sites.⁹ In liver Glucournyltransferase an enzyme binds this unconjugated bilirubin with glucuronic acid. This conjugated bilirubin (water soluble) can now be readily excreted in bile.¹⁰ In the term babies the normal lower limit of the serum albumin at the time of birth is 2.8gm/ dl.¹¹ In the developing countries like, Sub-Saharan Africa, Asia and Latin America, there is increased incidence of neonatal morbidity and mortality, attributed to neonatal jaundice (NNJ). Increase level of unconjugated bilirubin causes brain damage, kernicterus is a term for NNJ when it involves brain leading to neurological handicap and early death of affected infants.¹² kernicterus occurs when the molar bilirubin- to- albumin (B: A) ratio is >0.8.¹³ However, this can be avoided by the appropriate use of phototherapy and exchange blood transfusion to control serum bilirubin levels.¹² Most of the healthy term infants are discharged earlier because of medical, social and economic reasons. It has been observed that commonest cause for readmission during the early neonatal period is hyperbilirubinemia. Such readmissions exposes a healthy newborn to the hospital environment, causing emotional problems that involves extra expenses for both family and the institution along with the risks of poor breast-feeding.¹⁴ Hence early prediction of level of albumin in cord blood can not only be used for early detection of neonatal jaundice but can be helpful to prevent re-hospitalization of babies. It will also reduce the economic burden of re-hospitalization on family.

Materials and Methods

This study was carried out in Gynae/OBS department, neonatal intensive care unit , Pathology laboratory at Railway Hospital Rawalpindi in collaboration with the Biochemistry Department of Islamic International Medical College from June 2015 to March 2016. Ninety term neonates were selected and randomly divided in 3 groups with thirty neonates in each group. Term babies of both genders with any mode of delivery, Birth weight above 2000 gm, APGAR score over 7 and absence of significant illness or major congenital malformation were included in our study.

Babies having Significant illness (sepsis, RDS, asphyxia, IDM that could aggravate hyper

bilirubineia) Gestational age <37 weeks Birth weight below 2000 gm, Rh incompatibility were excluded from the study. After the informed consent of the parents 2 ml of blood was collected from the cord vein and serum was separated in the lab. Quantitative in vitro-estimation of serum albumin was done by calorimetric biuret method. Total bilirubin was estimated with jendrassik Grof method on photometric system - Micro Lab 300. 2 ml of cord blood was taken from the neoente with 5ml syringes and tranferred to gel tubes. All neonates were assessed for the appearnce of jaundice at time of discharge, and neonates who had serum albumins less than 3gm/dl amd bilirubin more than 1mg/dl were followed up from 7th till 20th post delivery day. Those babies who were physically jaundiced were re-admitted and their total serum bilirubin levels were repeated.

Depending upon their bilirubin levels all neonates in Group I with serum albumin less than 2.8 gm/dl, Group II with albumin between 2.8 - 3.3 gm/dl and Group III greater than 3.3 gm/dl were managed accordingly. All of our data was tested for normality. Kruskal –wallis test was performed to compare the parameters in between the groups, MannWhitney-U test was applied to compare the parameters within the groups. A *p*-value of < 0 .05 was considered significant. Correlation analysis was carried out using spaermans corelation test.

Results

In whole study group 86.7% neonates suffered from neonatal jaundice in group I and II 100% of neonates suffered from jaundice and in group III 60% had jaundice.

Table I: Median IQR of study groups on the basis of cord blood albumin and bilirubin concentration (n=90)

Biochemical parameters	Group I	Group II	Group III
Serum Albumin g/dl	2.0 (1.8 – 2.5)	3.1 (3.0 – 3.3)	4.5 (4.1 – 4.8)
Serum Bilirubin mg/dl	3.6 (2.7 – 3.9)	2.2 (2.1 – 2.6)	1.9 (1.8 – 2.1)

When compared by kruskalwallis a statistically significant difference of (*p*=0.00) was found, between all groups. when compared by using Mann-whitney U test a statistically significant difference of (*p*=0.00) was seen between group I and II and between group I and III. *P* value of (0.02) was found between group II and III.

Table II: Comparison of cord bilirubin in all groups by Mann-whitneyU test

Group	P Value
Group I	0.00
Group II	
Group I	0.00
Group III	
Group II	0.02
Group III	

phototherapy was to be given to 26.7% of the whole study population. In group I, 16.7 % received conventional phototherapy for the treatment of jaundice. In group II, 10.0 % received phototherapy. In group III, none of the neonate needed hospital intervention like phototherapy.

Table No III: Frequency distribution of phototherapy in all age groups

Phototherapy	Group I (n=30)		Group II (n=30)		Group III (n=30)	
	Frequency	Percentage %	Frequency	Percentage %	Frequency	Percentage %
Hospital Phototherapy	5	16.7	310.0	-		-
No phototherapy	-	-	-	-	30	0

Discussion

This study was commenced to distinguish the relation of serum albumin and bilirubin with neonatal jaundice. Cord blood albumin and bilirubin was measured after the delivery of neonates. A total of 90 neonates of both genders with weight ranging between 2 - 4 kg were selected. It was found out that all the neonates with low albumin and high bilirubin developed jaundice and 16.7% in group I and 10% in the group II received phototherapy and one neonate required exchange transfusion.

In this study it was found that neonate of group I with albumin less than 2.8 mg/dl developed jaundice within 72 hrs after birth and 16.7% required phototherapy in hospital. Sahu, et.al (2011)³ conducted a study on neonates and suggested that infants with low levels of albumin showed high bilirubin level and needed intensive phototherapy than those with high albumin level. Only one neonate from this group needed exchange transfusion and 83.3 % did not require any intervention like phototherapy or exchange transfusion.

None of the baby from group III with cord blood albumin greater than 3.3 gm/dl required

phototherapy or exchange transfusion. Sahu et al, in his study suggested that neonates with cord blood albumin level greater than 3 gm/dl require any interventional therapy or exchange transfusion.³

Our study showed that decreased serum albumin level leads to increased serum bilirubin level. This can be due to decreased availability of serum albumin to bind with bilirubin and transport it to excretory organs. Bairagi et al 2015, suggested that albumin has binding sites for bilirubin in subdomain 2A.¹⁵

Phototherapy has a standard role in treating neonatal hyperbilirubinemia. It lowers the serum bilirubin level as it uses light energy from the light source in altering the structure and the shape of bilirubin, converting bilirubin into isomers that are water-soluble and are not dependent on the process of conjugation for their elimination from the body. Even when normal conjugation is deficient it converts bilirubin to molecules that can be easily excreted. Bernaldo and Serge in one of their study stated that the neonates having bilirubin levels in the serum that are above 2 mg / dl have 53% of probability of receiving phototherapy.¹⁴

In our study, in group I about 16.7% neonates received phototherapy. In group II, a total of 10% received phototherapy. These results are in accordance with the results of the study done by Bernaldo and serge.¹⁴ In group III, none received phototherapy. This is supported by study done by Sahu et al.³ In addition to Phototherapy, exchange transfusion are extensively used world-wide for treating hyperbilirubinemia. It is considered as gold standard treatment for neonatal jaundice.¹⁶ In our study only one child required exchange transfusion due to raised bilirubin levels upto 20 gm/dl. M. Rahman in 2015 in one of his study suggested that neonates require exchange transfusion due to hyperbilirubinemia, septicemia or G6PD deficiency.¹⁷

Conclusion

The result of the present study revealed that the albumin taken from the cord blood immediately after the birth of the neonates can be used for the prediction of neonatal jaundice. It is further concluded that low albumin levels less than 2.8 gm/dl is not sufficient to bind with high level of bilirubin produced in neonates, leading to hyperbilirubinemia causing neonatal jaundice.

Further well designed research with large sample size is recommended for more clarification and assesment of relation of low level of albumin with neonatal jauindice.

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ORIGINAL ARTICLE

Testosterone Levels with Insulin Resistance in Type 2 Diabetes Mellitus in Men

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ABSTRACT

Objective: To determine the association of testosterone levels with insulin resistance in type 2 diabetes mellitus (T2DM).

Study Design: A Cross Sectional Observational Study.

Place and Duration of Study: This study was conducted at department of Chemical Pathology Army Medical College Rawalpindi from 11th Nov 2014 to 11th Nov 2015.

Materials and Methods: The study included 110 male participants. Two groups were made. Group A, included 55 patients of T2DM selected randomly from Endocrinology Department of Military Hospital Rawalpindi. Group B included healthy controls. Each group was further categorized on the basis of age and decade wise sub groups were made. Fasting plasma glucose (FPG), serum testosterone levels, serum sex hormone binding globulin levels (SHBG), glycosylated hemoglobin and fasting insulin levels were checked using fasting blood samples. The insulin resistance was calculated using Homeostatic Model for Assessment of Insulin Resistance (HOMA-IR). Data obtained was analyzed by SPSS version 20.

Results: Mean serum testosterone levels in group A (n=55) 9.36 ± 5.06 nmol/L was significantly lower ($P \leq 0.0001$) as compared to group B (n=55) 15.10 ± 6.99 nmol/L. Fasting plasma glucose (11.50 ± 3.35 vs. 4.23 ± 0.63 nmol/L), HbA1c (6.86 ± 0.35 vs. $5.05 \pm 0.45\%$), serum insulin (10.61 ± 4.87 vs. 5.71 ± 2.43 μ U/ml) and insulin resistance calculated by HOMA-IR (5.51 ± 3.73 vs. 1.07 ± 0.45) were significantly higher in group A as compared to group B.

Conclusion: The present study shows that a lower levels of serum testosterone are found in diabetic patients. Moreover there is significant negative correlation of serum testosterone with insulin resistance.

Key Words: Type 2 Diabetes Mellitus, Testosterone, Insulin Resistance, Homeostatic Model Assessment-Insulin Resistance.

Introduction

Diabetes mellitus (DM) is a metabolic disorder with inappropriate glycemic levels either due to absolute insulin secretion deficiency or reduction in the insulin effectiveness.¹ Several studies during the past few years have shown that male patients of T2DM have a significantly higher prevalence of low testosterone levels as compared to age matched healthy males.^{2,3} The Leydig cells of testes secrete male sex steroid hormone

testosterone (95%). It circulates either as free form (2%) or bound to albumin and sex hormone binding globulin (SHBG) in the serum. There are three phases of testosterone surge in a man's life i.e. during fetal life, shortly after birth and finally at puberty till 20 years of age, thereafter it starts decreasing with advancement of age.⁴ Testosterone exerts its physiological effects by activating androgen receptor either directly or through its metabolite 5 α -dihydrotestosterone (5 α -DHT).

Testosterone may also be aromatized to estradiol which in turn exerts its effects through estrogen receptor α (ER α).⁵ The bioavailable or free amount of testosterone depends on the level of SHBG as it is specific carrier protein of testosterone. Higher SHBG levels will result in free testosterone levels to be low. Conversely, SHBG lower levels will in turn

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cause free testosterone levels to be high. Free testosterone being the active form makes this relationship important. Thus men with normal total testosterone but high SHBG may have symptoms of low testosterone as free testosterone levels are low. Men with low testosterone have low metabolic rate hence are prone to develop obesity, which in turn leads to IR.⁶⁻⁸ Visceral adiposity also causes aromatization of testosterone to estradiol in fat cells. High circulating levels of estradiol will in turn suppress the production of testosterone causing its deficiency. Testosterone deficiency will then suppress lipolysis, reduce the metabolic rate leading to visceral fat deposition and insulin resistance.^{3,9,10} Hence a vicious cycle is initiated which plays the key role in pathogenesis of T2DM.

Low testosterone and diabetes often goes hand in hand. In fact men with T2DM are much likely to have low testosterone levels as men who don't have T2DM.^{11,12} Similarly numerous other studies have also highlighted IR and T2DM association with low serum testosterone levels.¹³⁻¹⁵

Such study has not been carried out in our population. Hence this study was planned to determine the association of testosterone levels with insulin resistance in type 2 diabetes mellitus (T2DM).

Materials and Methods

A cross sectional observational study was carried out at Chemical Pathology Department, Army Medical College Rawalpindi from 11th Nov 2014 to 11th Nov 2015. A total of 110 male individuals were included in the study by convenient sampling technique from the endocrinology department of Military Hospital Rawalpindi. They were divided into two groups. Group A consisted of 55 patients of T2DM and group B consisted of 55 healthy controls who had no major illness such as coronary heart disease, diabetes mellitus, thyroid disorders, and liver or kidney diseases. Each group was further categorized on the basis of age decade. Five ml venous sample was obtained from left median cubital vein after an overnight fast of 8-12 hours from the participants

under aseptic conditions. Centrifugation of the blood was done at 4000 rpm for 5 minutes for separation of plasma. Analysis of Fasting plasma glucose (FPG) was done on fresh plasma. Serum was frozen at -30°C for estimation of serum testosterone, insulin and SHBG levels. Two milliliter of whole blood was collected in Ethylenediaminetetraacetic acid (EDTA) containers for analysis of HbA1c.

Chemistry auto-analyzer Selectra E was used to measure FPG. Fully automated hormone analyzer, Immulite 1000, based on the principle of chemiluminescence immunoassay technique was used to measure serum testosterone, insulin and SHBG levels. HOMA-IR formula (FPG levels x Fasting Insulin levels/22.5) was used to calculate insulin resistance. Ion exchange resin method was used to estimate HbA1c levels. The data was entered on data base program SPSS version 20 and results of the test were subjected to appropriate statistical analysis. Independent t-test was used for comparing the quantitative data. Pearson's Correlation co-efficient was used to analyze the association of serum Testosterone with other variables. P-value of < 0.05 was considered statistically significant.

Results

A total of 110 participants were included in the study. Out of those 55 were diabetics and 55 were age and gender matched healthy subjects.

Comparison of biochemical profile of different

Table I: Comparison of the biochemical profile of the studied groups (n=110)

Variables (with reference range)	Group A (Diabetic) n=55	Group B (Control) n=55	P-Value
Testosterone(n mol/L) (8.86-36.47)	9.36±5.06	15.10±6.99	<0.001* *
SHBG (nmol/L) (13.3-90.0)	40.59±16.87	59.26±18.30	<0.001* *
FPG (mmol/L) (3.3-5.6)	11.50±3.35	4.23±0.63	<0.001* *
HbA1C (%) (4.0-6.0)	6.86±0.35	5.05±0.45	<0.001* *
Insulin (μIU/mL) (5-25)	10.61±4.87	5.71±2.43	<0.001* *
Insulin Resistance (<1.0)	5.51±3.73	1.07±0.45	<0.001* *

Note: *P-value<0.05, **=P<0.01

analytes in diabetic patients (Group A) and healthy controls (Group B) are summarized in Table I. The mean serum testosterone levels (mean \pm SD) in diabetic patients is 9.36 ± 5.06 nmol/L as compared to healthy controls 15.10 ± 6.99 nmol/L with significant p-value of <0.001 . The mean serum insulin levels

Table II: Comparison of testosterone levels at different age groups

Age (years)	Group A (Diabetic)	Group B (Control)	P-Value
30-40 (n=15)	9.01 ± 8.09	16.06 ± 7.78	0.022*
41-50 (n=11)	9.87 ± 4.06	14.59 ± 5.07	0.026*
51-60 (n=16)	8.75 ± 3.64	16.28 ± 9.65	0.007**
61-70 (n=13)	8.96 ± 1.38	12.08 ± 1.71	0.016**

Note: *P-value <0.05 , **P <0.01

(mean \pm SD) in diabetic patients is 10.61 ± 4.87 μ U/ml as compared to healthy controls 5.71 ± 2.43 μ U/ml with significant p-value of <0.001 . The insulin resistance of diabetic patients is significantly higher i.e 5.51 ± 3.73 as compared to healthy controls 1.07 ± 0.45 (P-value <0.001).

Comparison of serum testosterone levels at different

Table III: Correlation of testosterone levels with various parameters in diabetics

Age category	SHBG	FPG	HbA1c	Insulin	IR
Age (years)	r	r	r	r	r
30-40 (n=15)	-0.268	-0.044	-0.013	-0.311	-0.217
41-50 (n=11)	0.370	-0.358	-0.030	-0.058	-0.166
51-60 (n=16)	0.259	-0.441	-0.073	-0.433	-0.668
61-70 (n=13)	0.756	-0.053	-0.350	-0.111	-0.296

age groups in diabetic patients (Group A) and healthy controls (Group B) are summarized in Table II. Significantly lower levels of serum testosterone was noted in all age groups of diabetic patients as compared to healthy controls.

Correlation of serum testosterone levels with FPG, HbA1c, serum insulin and insulin resistance in different age groups of diabetic patients is

summarized in Table III. These results clearly shows significant negative correlation of serum testosterone with FPG, HbA1c, serum insulin and insulin resistance.

Discussion

This study was under taken to assess the association of testosterone levels with insulin resistance in type 2 diabetes mellitus in men. The principal observation of this study is that mean testosterone levels in diabetic patients is significantly lower as compared to the healthy controls. This finding is in agreement with studies carried out by Stellato et al, Goto et al, Ho et al and various others with similar results.¹¹⁻¹⁸ This study therefore establishes that serum testosterone levels are lower in type 2 diabetic males as compared to healthy controls.

Another important finding of this study is significant negative correlation of serum testosterone with insulin resistance. Serum insulin levels are much higher in diabetic patients as compared to healthy controls. Moreover there is significant insulin resistance in diabetic patients as calculated by HOMA-IR. This finding is also in agreement with studies carried out by Oh et al, Grossman et al and Goto et al.¹⁴⁻¹⁹ Another important observation of the study was negative association of fasting plasma glucose (FPG) and HbA1c with serum testosterone. This finding is in line with studies carried out by Dhindsa et al and Elsaygher et al.^{20,21}

The main limitation of our study is relative small sample size and financial constraints in carrying out costly endocrine tests. Further well designed studies with larger sample are suggested to assess the management strategies of T2DM to address the testosterone deficiency.

Conclusion

The present study shows lower levels of serum testosterone in diabetic (male) patients. Moreover there is significant negative correlation of serum testosterone with insulin resistance.

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ORIGINAL ARTICLE

Frequency and Characteristics of Ocular Trauma in Gilgit, Pakistan

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ABSTRACT

Objective: To study the frequency and characteristics of ocular trauma in Gilgit city, Pakistan.**Study Design:** Observational survey.**Place and Duration of Study:** This study was conducted at Gilgit Eye Hospital, Gilgit city from 1st January 2012 to 31st December 2012.**Materials and Methods:** It was an observational study (case series) concluded at critical analysis of data collected. Patients presenting with the complaints of ocular trauma over a period of one year were included in the study. Detailed history was recorded using a structured questionnaire including age, gender, occupation, month and the season, the place, nature of object, activity at the time of injury and time lapsed after trauma and presentation at the hospital.**Results:** Patients ranged from 2 years to 75 years, with a mean age of 44.07±13. Majority of the patients were males (62.61%). The age group range in 36.9 % of the patients was 31-45 years and 15-30 year in 22.4 % of the patients. The patients who presented within one hour after an eye injury were 45.32%. The highest number of injuries occurred in the summer season (52.7%). The most common cause of eye injury in the study group was related to wood cutting (19.1%). The commonest place where injury occurred was in woods and mountains (17.7%). The activity which was common at the time of injury was cutting wood followed by playing out door games. Most of the patients suffered from blunt trauma and had closed eye injuries (81.3%). Most of the patients had good visual acuity at presentation (6/6 to 6/18 in 39.3%). The commonest types of injuries were Periorbital swelling, ecchymosis and subconjunctival hemorrhages (40.1%). The cases were managed according to the clinical findings and investigations.**Conclusion:** This study highlights the pattern and characteristics of ocular trauma presenting to an eye facility in Gilgit city. The frequency of ocular trauma is more in young males, mostly blunt, unilateral and work related. Majority of the ocular injuries are caused by wood and rocks in the mountains. Children suffer from ocular trauma at home and schools while playing games and sports.**Key Words:** Ecchymosis, Ocular Trauma, Ocular Injury, Periorbital Swelling, Subconjunctival Hemorrhages

Introduction

Trauma to the eye and its surrounding structures is a leading cause of visual morbidity and blindness.¹ Even though, ocular trauma has been described as a neglected issue, it was highlighted as a major cause of visual morbidity more recently.² According to World Health Organization estimation, 55 million ocular injuries occur each year. A rough estimate is that one out of every twenty patients examined by

an ophthalmologist is suffering from ocular injury.³ Ocular trauma is considered to be one of the preventable causes of blindness in the world but annually 1.6 million people still become blind from ocular trauma.¹ The data available in the developing countries about ocular trauma is limited and does not indicate the magnitude of the problem, the risk factors, the circumstances and the population at risk.⁴ The limited available data is not admissible for every region as factors vary according to every city and region.

Gilgit city is located in the northern region of Pakistan having mountainous terrain, agricultural plains and tourist's recreational areas. People here belong to different customs and practices as compared to the rest of the country. Till now no research has been done in the study area on ocular trauma. We carried out this observational survey to know the frequency and characteristics of ocular trauma in Gilgit city with the hope that it may prove helpful to find preventive methods for minimizing such disabling injuries.

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Hence, this data may be representative for any of the surrounding region.

Materials and Methods

It was an observational survey conducted at Gilgit Eye Hospital, Gilgit from 1st January 2012 to 31st December 2012 that concluded at critical analysis of the collected data. The principles outlined in the Declaration of Helsinki (2008) were followed to conduct the study. With informed consent, data was collected from all the patients presenting with the history of ocular trauma at Gilgit Eye Hospital. Detailed history was recorded using a structured questionnaire including age, gender, occupation, the month and season, the place, nature of object, activity at the time of injury and time lapsed after trauma and presentation. The author recorded the details of anterior segment by slit lamp biomicroscopy, examined the posterior segment after dilating the pupils (using direct and indirect ophthalmoscope) and measured the intraocular pressure by Applanation Tonometer. All the ophthalmic findings were recorded on a proforma. To rule out intraocular foreign body, X-rays orbit (posterior-anterior and lateral view) and ultrasonography were carried out where and when required. All the cases were managed according to the ophthalmic findings. Data was entered and analyzed using the SPSS version 22. The age was analyzed by descriptive method with range and mean \pm SD where as the qualitative variables were analyzed as frequencies and percentages.

Results

During the study period a total of 23179 patients with ocular complaints presented to the hospital among which 214 patients reported with the complaints of ocular injury (0.92%). Majority of the patients were males (62.61%), male to female ratio was 1.67:1. The presentation of the patients varied throughout the year; highest number of presentation was in the summer season (52.7%), followed by in spring season (30.8%) and least in the winter season (7.9%). The time elapsed between injury and presentation to the hospital was also noted. Around 66.82% of the patients presented within 24 hours after the injury, whereas 5.1% of patients presented with more than one year history of ocular trauma.

Patients ranged from the age of 3 years to 75 years with mean age of 44.07 ± 13 . The patients were divided into age groups of 3-14, 15-30, 31-45, 46-60 and 61-70 years. It was found that maximum number of patients i.e. 36.9% belonged to 31-45 age group, 22.4% were of age group 15-30 whereas 12.6% were in 3-14 age group. Table No. I shows the occupations of the study group.

Table I: Distribution of Patients according to their Occupation (n=214)

Occupation	No of Patients
Student (school/seminary)	29 (13.5%)
Miner/ Brick layer/Construction Worker	25 (11.6%)
Farmer / Sheppard	24 (11.2%)
Toddlers and infants	23 (10.7%)
Woodcutter /Saw miller/ Carpenter	23 (10.7%)
House Wife	16 (7.5%)
Motor Mechanic / Electrician / Welder	16 (7.5%)
Public Transport Drivers	16 (7.5%)
Teacher (school/seminary)	13 (6%)
Trader	9 (4.2%)
Retired	9 (4.2%)
Health Professional	7 (3.2%)
Office Job	4 (1.8%)

The most common cause of injury in the study group was related to wood (19.1%) followed by gunshot or pallet injury in 12.1% of the patients. (Table No. II)

Table II: Various Causes of Ocular Trauma (n=214)

Causative Agent	Male	Female	Total
Thorn /Tree Branch/Wood	23(10.7%)	18(8.4%)	41(19.1%)
Gunshot /Pallet	23(10.7%)	3(1.4%)	26(12.1%)
House Hold Utensils (Broom, Sewing Needles, kitchen Items)	5(2.3%)	18(8.4%)	23(10.7%)
Rocks /Stones (projectile /non projectile)	17(7.8%)	4(1.9%)	21(9.8%)
Pocket Knife/ Hunter Knife /Blade /Screw Driver	18(8.4%)	1(0.5%)	19(8.9%)
Animal Horn / Hoof	7(3.2%)	10(4.7%)	17(7.9%)
Fall / Wall Hit /Door Hit	4(1.9%)	10(4.7%)	14(6.5%)
Broken Glass (bottles ,windows, wind screen)	8(3.7%)	5(2.3%)	13(6%)
Hit by Slap /Fist /Nail /Cane	7(3.2%)	5(2.3%)	12(5.5%)
Sports gear	10(4.7%)	1(0.5%)	11(5.1%)
Pencils /pens	4(1.9%)	5(2.3%)	9(4.2%)
Vehicle Hit/ crash	8(3.7%)	0(0%)	8(3.7%)

The commonest place where injury occurred was in woods or mountains (Table No. III), accounting for 38 patients (17.7%). 25 patients sustained injury while in the playground and 21 patients were at school. Highway or road side trauma was in 5.6% of the patients.

Table III: Location Where the Ocular Injury Occurred (n=214)

Place of Injury	No. of Patients
Mountains /Woods	38(17.7%)
Fields/Farm	33(15.4%)
Home	27(12.6%)
Play Ground	25(12.6%)
School	21(11.6%)
Public Building	20(9.3%)
Office/Shop	19(8.8%)
Garage / Workshop /Construction Site	19(8.8%)
Highway /Road side	12(5.6%)

The activity which was commonest at the time of ocular injury was cutting wood, followed by playing games (Table No. IV).

Closed eye injuries were in 81.3% of the patients. Right eye involvement was in 52.3% and in 2.3% it was bilateral. On examination, 84(39.3%) patients had good visual acuity at presentation (6/6 -6/18) and 23(10.7%) patients presented with visual acuity < 3/60.

Table IV: Activities at the Time of Ocular Injury (n=214)

Activity	No of patients
Cutting Wood	31(14.5%)
Playing / Running /Walking	29(13.5%)
Fighting	28(13%)
Household Tasks	24(11.2%)
Farming	20(9.3%)
Standing	19(8.8%)
Helping / Learning	19(8.9%)
Driving/Travelling	17(7.9%)
Repairing / Constructing	15(7%)
Reading /Gazing	7(3.2%)
Writing/ Typing	5(2.3%)

The most common (40.1%) type of eye injuries were periorbital swelling, ecchymosis and subconjunctival hemorrhages combined (Table No. V). Then were corneal foreign body /abrasion (19.6%) followed by

traumatic cataract /dislocated lens (18.2%), lid tears (15.4%), Hyphema (1.5%) and Uveal prolapse (5.1%). We found corneal ulcers in 17 patients, retinal detachment and intraocular foreign body in 12 and tears (corneal, scleral, corneoscleral) in 11 patients. We also found corneal opacities, corneal abscesses and endophthalmitis in our patients. There were 4 cases of multiple ocular structure damage, 2 cases had optic atrophy, one had ptosis and one had a blow out fracture.

Table V: Ophthalmic Findings after Ocular Trauma (n=214)

Ophthalmic findings	Male	Female	No of Patients
Periorbital Swelling /Ecchymosis/Sub Conjunctival Hemorrhage	49(22.9%)	37(17.3%)	86(40.1%)
Corneal Foreign Body /Abrasion	36(16.9%)	5(2.3%)	42(19.6%)
Cataract /Dislocated Lens	32(15%)	7(3.2%)	39(18.2%)
Lid Tear/ Ectropion	18(8.4%)	15(7%)	33(15.4%)
Hyphema	23(10.7%)	6(2.9%)	29(13.5%)
Corneal / Scleral /Corneoscleral Tear	18(8.4%)	1(0.5%)	19(8.9%)
Corneal Ulcer	8(3.7%)	9(4.2%)	17(7.9%)
Flat Anterior Chamber	15(7%)	1(0.5%)	16(7.5%)
Corneal Edema	7(3.2%)	5(2.3%)	12(5.6%)
Uveal Prolapse	9(4.2%)	2(0.9%)	11(5.1%)
Corneal Opacity	3(1.4%)	6(2.8%)	9(4.2%)
Corneal Abscess	2(0.9%)	5(2.3%)	7(3.2%)
Endophthalmitis	3(1.4%)	4(1.9%)	7(3.2%)
Macular / Retinal Edema	5(2.3%)	2(0.9%)	7(3.2%)
Retinal Detachment	7(5.6%)	0	7(5.6%)
Iris Dehiscence	3(1.4%)	3(1.4%)	6(2.8%)
Intraocular Foreign Body	5(2.3%)	0	5(2.3%)
Raised Intraocular Pressure	3(1.4%)	2(0.9%)	5(2.3%)
Phthisis Bulbi	1(0.5%)	3(1.4%)	4(1.9%)
Multiple Ocular Structure Damage	4(1.9%)	0	4(1.9%)
Optic Atrophy	0	2(0.9%)	2(0.9%)
Ptosis	1(0.5%)	0	1(0.5%)
Blow Out Fracture	1(0.5%)	0	1(0.5%)

The cases were managed according to the clinical findings and investigations. Adenexa and anterior

segment injuries requiring surgical intervention were operated. The cases requiring posterior segment surgery, corneal opacities with potential of visual improvement, patients with phthisis bulbi and one case with blow out fracture were referred to the appropriate centers. Patients having no visual potential were counseled and those in need were referred for rehabilitation with low vision aids.

Discussion

In this study we found the magnitude of ocular trauma to be 0.92% in relation to the total patients presenting to the hospital. It is comparable to the findings of the study conducted in Karachi.⁵ But it is significantly low as compared to the findings of a study done at JUDO, south west Ethiopia,¹ where it was found to be 6.9%. We found bilateral eye involvement in 2.3% cases while Karaman K⁶ has given figures of bilateral involvement in 3.7% and Khan MD⁷ has given figure of 4.9%. In this study closed globe injuries were found to be more common than open globe injuries accounting for 81.3% of patients. Arfat M Y⁸ also reported blunt ocular trauma to be most frequent whereas Karaman K found 67.3% were closed and 32.7% were open globe injuries in his study.⁶

This study shows a male predominance. Many studies have shown that; males who are in the active and economically productive age (30 to 45 years), tend to have more eye trauma as compared to females.^{2, 3, 5} This may be due to the fact that young males are more likely to be involved in hazardous activities either work-related or related to sports and 30 to 45 years age being more volatile and less responsible.⁹

According to Jan S, 60.75% ocular emergencies were below 20 years of age.¹⁰ Okeigbemen VW stated that 44.8% of his patients suffering from ocular trauma were dependants (toddlers, pupils and students).¹¹ In comparison to these incidences in our study 35 % of patients were less than 15 years (13.5% students and 10.7% toddlers and infants). These are alarming figures which need to be addressed because according to Dandona L et al majority of the trauma resulting in blindness occurs during childhood and young adulthood.¹²

We found that ocular trauma occurred in 12.6 % cases at home though higher incidences have been reported in other studies. Babar TF reported that

most of ocular trauma took place at home¹³ and according to Mowatt L home is the most common place for eye injury.¹⁴ In our study, 11.6% cases suffered ocular trauma at school and Oluyemi F have reported in 5.9%.¹⁵ These incidences are alarming as home and schools thought to be safe are on the contrary. Moreover such accidents are probably underreported. 12.6% of our patients suffered an ocular trauma while in play ground and 5% cases suffered from sports gear related ocular injury. Augmenting our findings are reports by Tsedeke A¹ who reported sports related ocular injury in 7.3% and by Jan S who noted that ocular trauma during playing games was in 66.66% and in 27.77% it was with sports gear related.¹⁰

Knyazer B et al reported that most of the injuries are work related.¹⁶ In any occupation, ocular injuries can occur at random but some occupations are always at risk of sustaining eye injury. Occupations like mining; construction work, wood cutting, carpenter, motor mechanic and welding are exposed to hazardous conditions and can suffer from trauma. In our study 40.7% of the ocular trauma was work related. Our setting, being a mountainous area, people are more involved in occupations related to wood, mining and farming. Therefore are prone to occupational hazards. We had ocular trauma with wood (19.1%), stones (9.8%) and knives/ screw drivers (8.9 %) signifying the need of providing preventive care to the workers and necessary gear for prevention. Similarly animal handlers who sustained ocular injuries (7.9% in our study compared to Enock ME 19.2%) need education regarding non hazardous animal care.¹⁷ Furthermore there were bus drivers and pedestrians who suffered from highway /road side accidents and there were others, being retired and health professional that were exposed to either violent conditions or domestic accident. Other researchers have reported the same. Enock ME¹⁷ reported that ocular trauma caused by road traffic accident and assault was in 30.8% and 22% respectively. Tsedeke A¹ reported that violence caused ocular injury in 37.2% and domestic accidents in 29.2% of cases.

The causes of injury, although remained variable in all the cases, most common was related to wood and rock. Researchers have augmented our findings. Oluyemi F¹⁵ reported the common mechanism of

injury was from a chip of metal or vegetative matter impacting the eye. Jan S¹⁰ reported 44.44% cases received ocular trauma with stone and Omolase CO et al reported that vegetative materials were the most common offending agent.¹⁸

According to Rahman I, good visual acuity at presentation is correlated with good visual outcome.¹⁹ In our study 39.3% patients had good visual acuity at presentation (6/6 -6/18). Patients who presented less than 1 hour after ocular injury were 45.32% where as 5.1% presented as late as one year after ocular injury. In the JUDO study 31.6 % patients presented within 48 hours whereas 28.6% arrived after one week or later.¹ In a study by Enock ME delayed presentation was more common.¹⁷ 22 patients presented within 24 hours of injury and 63.61% patients presented after one week. The prognosis of vision is adversely affected by delay before proper management or presentation to the hospital and by administration of inappropriate treatment.¹³ The delay in presentation can lead to complications like phthisis bulbi, optic atrophy and endophthalmitis as found in our study.

Oluoyemi F¹⁵ reported corneal wounds (43.7%) or corneo-scleral (41.5%), Uveal prolapse in 68.1%, hyphema in 47.4%, and cataract in 28.1% in his study. We found corneal involvement in 19.6%, lens involvement in 18.2%, hyphema in 1.5% and uveal prolapsed in 5.1%.

The presentation of the patients varied throughout the year. There were more cases of ocular trauma in summer season as compared to winter due to the extreme cold weather. Karaman K⁶ also reported that the majority of injuries occurred during July, August, and September and the frequency was lowest in February and November (5.7%). The reason being, because of snow fall and people get more confined to their homes, children are out of school and people are less involved in outdoor activities.²⁰

There are certain limitations of our study; as the study is based on data from a particular hospital and it is not a population based; hence does not give a true measure of the incidence and prevalence of ocular trauma in the population of Gilgit city. The comparison of our study data with the studies reviewed was difficult in many aspects due to non similar classifications and different reporting methods but it might be helpful for further

population based studies and prevention of ocular trauma.

Conclusion

This study highlights the pattern and characteristics of ocular trauma presenting to an eye facility in Gilgit city. The frequency of ocular trauma is more in young males, mostly blunt, unilateral and work related. Majority of the ocular injuries are caused by wood and rocks in the mountains. Children suffer from ocular injuries at home and schools while playing games and sports. Attention should be aimed at preventing ocular trauma at workplace, home and schools.

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ORIGINAL ARTICLE

Effects of Thoracic Spine Mobilization on Vitals and Blood Oxygen Level in Healthy Individuals

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ABSTRACT

Objective: The objective of this study was to determine the effect of thoracic spine mobilization on heart rate, respiratory rate, blood pressure and blood oxygen saturation.

Study Design: It was a quasi experiment study.

Place and Duration of Study: The study was conducted in the department of Physical Therapy and Rehabilitation Center, Pakistan Railway Hospital Rawalpindi. The duration of study was 04 months from July 01 to October 30, 2015.

Materials and Methods: Ninety six healthy adult individuals were selected for the study by convenient sampling technique. The inclusive criteria of healthy individuals aged 20-60 years with normal vitals; Blood Pressure: 90/60 mmHg Diastolic, 140/100 mmHg Systolic, Breathing: 12-25 breaths per minute, Pulse: 60 - 120 beats per minute and Temperature: 98.6 degrees Fahrenheit. Subjects with spinal injury or deformity were not included in the study. Pre and post values of heart rate, respiratory rate, blood pressure and blood oxygen saturation after thoracic spine mobilization were obtained. The data were statistically analyzed by SPSS version 21.

Results: Mean age of the study population was 27.9±4.7, male to female ratio was 1:1. Majority of the study participants (45%) had normal BMI. Thoracic spine mobilization caused significant change in oxygen saturation. The Heart Rate (HR), Respiratory Rate (RR), both systolic and diastolic blood pressure (BP) had no significant association with the age, gender or the BMI of study participants. However blood oxygen saturation showed a statistically significant association with above mentioned variables.

Conclusion: It is concluded that mobilization on thoracic spine (T1-T4) causes a sudden elevation in heart rate, respiratory rate, blood pressure and no major change in blood oxygen saturation.

Key Words: Blood Pressure, Heart Rate, Manual Therapy, Respiratory Rate, Thoracic Spine Mobilization.

Introduction

The mobilization of the spine specially thoracic spine not only activates the mechanoreceptor inside the capsule of face joint which regulate the intrinsic muscle control of the spine but also have some influence to activate the sympathetic nervous system(SNS). As we know the sympathetic part of the autonomic nervous system (ANS) regulate heart

rate, blood pressure, rate of respiration, body temperature, sweating, gastrointestinal motility and secretion, as well as other visceral activities that maintain homeostasis. The sympathetic system prepares the body for energy expenditure, emergency or stressful situations, i.e., fight or flight. Sympathetic preganglionic neurons are shorter than sympathetic postganglionic neurons.¹ Most organs receive innervations from SNS and Peripheral nervous system (PNS), which usually have opposing actions. However some organs do not have a response to parasympathetic stimulation.² Control of lung primary ventilation involve specific groups of receptors.³ Resistive load on breathing in a healthy subject can stimulate aortic baroreceptors and subsequently causes an impact on the ANS.⁴

In a study carried on patients with chronic neck pain, respiratory functions of the subjects in terms of forced vital capacity (FVC), forced expiratory volume at one second (FEV1), and peak expiratory flow (PEF) were measured via Cardio Touch equipment after thoracic mobilization and self-stretching exercises.

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The results of the study indicated that thoracic mobilization is effective treatment strategy for improving pulmonary functions.⁵ Reduction in lung function may be due to thoracic spine motion and costochondral joint restriction might affect the functions of respiratory system. When hypomobility of the joint is identified, joint mobilization techniques are applied that may influence in improving lung function. Physical therapeutic approaches for the thorax include thoracic mobilization, stretching of the respiratory muscles, and strengthening of the respiratory muscles. Such respiratory rehabilitation reduces respiratory problems in patients with respiratory dysfunction. Autonomic output to the heart may be influenced by high velocity and low amplitude manipulations of the thoracic spine.⁶ Physical therapy can promote effective health outcomes by minimizing the deleterious effects of pathological conditions, including the Coronary Artery Disease, Arterial Hypertension (HTN), Diabetes Mellitus, Atherosclerosis, Osteoporosis, Alzheimer and Parkinson's disease.⁷ Physiotherapists frequently apply spinal manipulative therapeutic techniques to relieve pain syndromes of musculoskeletal origin and to enhance the joint movement quality. In a study, grade III mobilization technique in posterior-anterior direction was centrally applied to the cervical spine; as a result both respiratory and cardiovascular values were affected. During the application of the technique there was a significant increase in respiratory rate, heart rate, systolic and diastolic blood pressure when it was compared with control group.⁸ Manual therapy intervention to the thoracic spine was able to modify heart rate variable in women with Fibromyalgia. Considering this we can justify that there is a correlation between autonomic dysfunction and symptom severity or quality of life of the patients. Some studies have shown that spinal manipulation is able to modulate autonomic nervous activity. Yates et al⁹ examined the effect of chiropractic manipulation of T1–T5 spine segments in patients with Arterial Hypertension. He observed a reduction in systolic and diastolic blood pressure and anxiety level. Brain budgell et al in 2006 used high-velocity and low-amplitude manipulation of the thoracic spine which showed a different result in output of heart as compared to sham procedure

group.⁶ Elderly people can improve and maintain their cardiopulmonary circulation and also increase their oxygen intake through continuous physical training. In a society where aging is becoming a longer process due to increased average life expectancy, research on interventions to improve respiratory function in the elderly should be actively conducted.⁹

The anatomical relation of thoracic spine with the sympathetic nervous system is well defined and most of the studies showed the relationship of manual therapy effects on SNS. In Pakistan no such study has been conducted to find the relationship of thoracic spine mobilization and SNS in healthy individuals or the patients having cardiac or other associated problem. From clinical perspective it is advised that physical therapist should take special consideration of patients while applying thoracic mobilization. The result of this study will create awareness regarding the fruitful effects of thoracic mobilization on cardiovascular and pulmonary system. The purpose of this study is to determine the effect of thoracic mobilization on Heart rate, Respiratory rate, BP and blood oxygen saturation.

Materials and Methods

It was quasi experimental study done in the department of Physical Therapy and Rehabilitation Center, Pakistan Railway Hospital Rawalpindi. The duration of study was 04 months from July 01 to October 30, 2015.

Ninety Six healthy individuals having age between 20 to 60 years with normal vitals, Systolic BP 140/100 mm of Hg, Diastolic BP 90/60 mm of Hg, Breathing: 12 - 25 breaths per minute, HR 60 - 120 beats per minute and Temperature 98.6 degrees Fahrenheit were selected for this study. Those who had abnormal vitals, any previous spinal injury or surgery, spinal deformities were excluded from the study.

In order to determine the effect of thoracic mobilization on heart rate and respiratory rate, self-designed questionnaire was used and data was collected by the therapist himself. Informed consent was taken from every subject prior to participation in study. Only participants who were vitally stable were given Kaltenborn grade 3 thoracic mobilizations. Heart rate, respiratory rate and other readings were taken before thoracic mobilization. 5 set with 15 repetitions were given on thoracic spine (T1 to T4

Level) with the gap of 10 to 15 seconds. After thoracic spine mobilization again heart rate, respiratory rate and other readings were measured again. The telemetry operon OM12 apparatus was used for measuring pre and post readings. The telemetry operon OM12 complete built-in module design ensures stable and reliable performance, unique all-lead ECG on-one-screen display, which can facilitate the diagnosis and analysis of cardiac disease. The oxygen saturation was measured through digital pulse oxy meter. Questionnaire consisted of two components, the first component comprised of 10 questions to assess the physical fitness of the subjects. The second component was used to measure the pre and post variables readings. The data was analyzed using SPSS 21 software. Paired *t* test was applied to compare the pre and post mean difference and p-values.



Fig 1: Collecting initials and final readings through telemeter



Fig 2: Thoracic spine Mobilization

Results

The mean age of participant was 27.9 ± 4.7 , male to female ratio was 1:1 and majority of the subjects had normal BMI. (Fig 3)

As shown in Table I, after thoracic spine mobilization the pre and post mean values of heart rate, respiratory rate, systolic and diastolic BP, and blood oxygen saturation shows a statistically significant difference.

As shown in the Table II the HR, RR, Both systolic and Diastolic BP have no significant association with age, gender or the BMI of study participants. However blood oxygen saturation shows a statistically significant association with above mentioned variables.

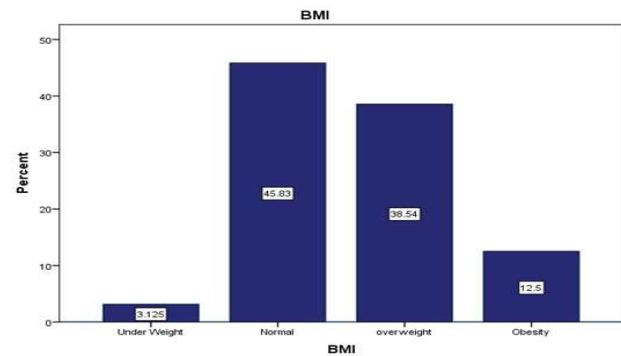


Fig 3: BMI of the Participants

Table I: Pre and post mean value of Heart rate, Respiratory rate, Systolic blood pressure

Variables	Pretreatment Mean \pm SD	Post Treatment Mean \pm SD	Mean Difference	% Difference	P value
Heart Rate	81.72 \pm 7.017	88.36 \pm 9.37	6.63542 \pm 6.25	8.1	.000*
Respiratory Rate	15.67 \pm 1.80	18.15 \pm 2.30	2.48958 \pm 2.50	15.8	.000*
Systolic Blood Pressure	122.79 \pm 8.77	124.64 \pm 6.19	1.85417 \pm 7.12	1.50	.012*
Diastolic Blood Pressure	77.38 \pm 6.44	78.91 \pm 5.81	1.53125 \pm 3.08	2.08	.000*
Blood O ₂ Saturation	96.87 \pm 1.27	97.34 \pm 2.28	.46875 \pm 2.19	0.47	.039*

Table II: Association of Heart rate, Respiratory Rate, Systolic and Diastolic Blood Pressure and Blood Oxygen Saturation with age, gender and BMI

Variables	Vs	Value	Asymp. Sig. (2-sided)
Heart Rate	Age	74.408 ^a	.969
	Gender	40.228 ^a	.181
	BMI	82.486 ^a	.885
Respiratory Rate	Age	33.961 ^a	.282
	Gender	14.759 ^a	.141
	BMI	34.790 ^a	.250
Systolic blood Pressure	Age	99.043 ^a	.010*
	Gender	20.240 ^a	.627
	BMI	82.151 ^a	.133
Diastolic blood Pressure	Age	82.352 ^a	.130
	Gender	20.904 ^a	.587
	BMI	69.848 ^a	.449
SPO2	Age	30.920 ^a	.009*
	Gender	19.507 ^a	.002*
	BMI	27.622 ^a	.024*

Discussion

The results of present study showed that thoracic spine mobilization resulted in sudden elevation of HR, RR, Systolic and diastolic BP and blood oxygen level in healthy individuals. The blood oxygen saturation showed significant relation with age, gender and BMI.

It provides objective evidence that application of mobilization technique elicits change in SNS. The previous studies show that spinal mobilization and manipulation causes marked effect on HR and RR. Reis MS et al saw the effect of thoracic posteroanterior thoracic mobilization on heart rate variability; they also concluded that one session of Maitland mobilization on thoracic spine decreases the HR from 81 ± 10 to 77 ± 9 and improves pain on NPRS from 6 ± 1 to 4 ± 1 . Similarly, in this study, difference (8.1%) in heart rate was observed before and after posteroanterior mobilization i.e. an increase in heart rate was noticed after thoracic mobilization.¹⁰

Ward J et al (2013) observed the effect of upper thoracic spine manipulation on cardiovascular response; their study shows that cardiovascular physiologic response is not affected in the short term by anterior upper thoracic spine chiropractor mobilization/manipulative therapy in young normotensive individuals. Contrary to this, the study depicted short term effect after thoracic mobilization on cardiovascular system.¹¹ Yung e Et al (2014) observed the blood pressure and heart rate response to anterior to posterior directed glide to spine in young pain free individuals. This study showed that the AP glide caused the statistically significant response that results in a minor drop in HR as compared to placebo group. In both groups, there was a small but statistically significant reduction in systolic BP after thoracic mobilization.¹² McGuiness j et al (1997) observed the influence of a cervical mobilization technique on respiratory and cardiovascular function results shows significant increase in respiratory rate, heart rate, systolic and diastolic blood pressure.¹³

Conclusion

It is concluded that mobilization on thoracic spine T1-T4 will cause a sudden elevation in HR, RR, BP and

blood oxygen saturation. There is a significant relation of blood oxygen saturation with age, gender and BMI.

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ORIGINAL ARTICLE

Hepatoprotective Effect of Acetylated Amino Acid on Methimazole Induced Hepatotoxicity in Mice

Zunera Hakim¹, Akbar Waheed², Aroosa Ishtiaq³, Wardha Mazhar⁴

ABSTRACT

Objective: To explore the hepatoprotective effect of N-acetylcysteine on methimazole induced hepatic damage in mice.

Study Design: Randomized control trial.

Place and Duration of Study: The study was carried out from Nov 2014 to Oct 2015 at the animal house of Army Medical College, Rawalpindi.

Materials and Methods: Thirty male BALB/c mice were randomly divided into three groups of ten animals each. Group I: Control group (C), Group II: Methimazole treated group (M), Group III: Pretreated N-acetylcysteine (NAC) group. Single dose of Methimazole (MMI) (1000mg/kg, i.p) was injected for induction of hepatotoxicity. N-acetylcysteine (NAC) (300mg/kg, i.p) was given pre Methimazole (MMI) administration. The extent of hepatic injury was determined by evaluation of serum alanine transaminase (ALT) and alkaline phosphatase (ALP) along with liver histopathology.

Results: Methimazole (MMI) produced liver damage as evident by markedly raised liver enzymes along with necrosis and inflammatory cell infiltration. N-acetylcysteine (NAC) treated group resulted in reduction in elevation of serum biomarkers and improvement of histological picture.

Conclusion: N-acetylcysteine (NAC) holds significant hepatoprotective effect against Methimazole (MMI) induced hepatotoxicity.

Key Words: *Methimazole, Hepatotoxicity, N-acetylcysteine.*

Introduction

Methimazole (MMI) is the most frequently prescribed antithyroid drug worldwide.¹ The preferred use of MMI for hyperthyroidism can be attributed to its better compliance and superior safety profile. However, its clinical use is associated with many extra thyroidal toxicities including hepatotoxicity which limit its usefulness. MMI induced hepatic injury has an incidence of 6.6% in adults presenting as hepatitis, cholestasis and acute liver failure.^{2,3} Liver injury produced by MMI is dependent upon bio activation to its reactive metabolites i-e N- methylthiourea and glyoxal. These

intermediates cause oxidative and carbonyl stress, mitochondrial impairment and immune reactions.⁴ Previous studies have also identified cellular glutathione as an important susceptibility factor in MMI induced cytotoxicity.⁵

Despite reports of MMI induced liver damage, no specific protective has been developed against it. However, an indisputable area of medicinal benefit involves attenuation of oxidative hepatic damage. Researches have recognized the role of antioxidants in various types of drug induced liver injuries.⁶ N-acetylcysteine; the acetylated non enzymatic antioxidant has been the antidote for acetaminophen poisoning since 1974. However, its safety and efficacy has been proven outside acetaminophen overdose in liver transplant related damage, fibrosis, hepatitis, alcoholism, heavy metal toxicity and wide range of glutathione deficient genetic and metabolic disorders.⁷ NAC exerts its beneficial effects in these clinical settings through glutathione dependent and independent mechanisms.⁸

The aim of the conducted study was to explore the protective effect of NAC against MMI induced hepatotoxicity in mice.

Materials and Methods

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An experimental study was carried out at the Animal house of Army Medical College, Rawalpindi from Nov 2014 to Oct 2015. The conducted trial was a joint venture of Department of Pharmacology and Therapeutics and Department of Pathology, Army Medical College. Thirty male 8-10 weeks old BALB/c mice, weighing 30-40 gram were provided by National Institute of Health, Islamabad. Mice were housed under standard husbandry conditions (temperature $20 \pm 2^{\circ}\text{C}$, humidity 40-60% and 12 hour light/dark cycle) with diet, water and libitum. Animal care and research was carried out in accordance with protocols of ethical committee of "Centre of Research in Experimental and applied Medicine (CREAM)".

MMI of analytical grade was purchased from Sigma Chemicals USA through a licensed dealer. NAC injections of Aumur Pharmaceuticals were purchased from Karachi based pharmacy.

Only adult healthy male mice weighing > 30 grams and < 40 grams with normal LFTs and no obvious abnormality were included in the study. After one week of acclimatization mice were randomly divided into three groups with ten animals each. Group I (n=10) served as the control group (C) and was given normal saline intraperitoneally (i.p). Group II was MMI treated group (M) and given MMI dissolved in normal saline (1000mg/kg i.p). 1000 mg/kg i.p of MMI was taken as the appropriate toxic dose after conduction of pilot study with various previously mentioned experimental doses.^{9,10} Group III; NAC pretreatment (NAC -Pre) group was intervened with NAC (300 mg/kg i.p) one hour before MMI.¹¹

Baseline sampling of all animals was done through tail vein obtaining at the start of research.^{12, 13} After recommended recovery period¹⁴, intervention was carried out and blood samples were collected by performing cardiac puncture five hours after MMI administration.¹⁰ Serum obtained from clotted blood by centrifugation at 3000 revolution/min was used for analysis of ALT and ALP by commercially available kits of Cormay and Linear. ALT was estimated by IFCC method while calorimetric method (DGKC method) was applied for ALP. At the end of experimental period, liver was removed and fixed in 10% formalin. Hematoxylin and eosin (H&E) stained slides were prepared and studied under microscope for histopathological findings.

Data was analyzed using SPSS 21. All data was expressed as Mean \pm S.E.M. Statistical difference between serum markers at initial and final hours was calculated using students t- test. One way ANOVA followed by Post hoc Turkey was applied for multiple comparisons between groups. $p < 0.05$ was considered significant.

Results

Effect of N-Acetylcysteine on Serum ALT Levels

Baseline and final values of ALT of G-I (control group) and G-III (NAC pretreated group) remained within normal range during the experimental period (Fig 1). An insignificant p value was obtained when G-I was compared with G-III (Table II). MMI significantly raised ALT levels (261.33 ± 20.30) as compared to initial values (45.33 ± 9.84) (Fig 1) and control Group I. (Table I). NAC affords protection against MMI induced hepatic insult by mitigating the rise in ALT as evident by significant difference between G-II and G-III (Table III).

Effect of N-Acetylcysteine on Serum ALP Levels

Results revealed an insignificant difference between initial and final levels of ALP of G-I and G-III (Fig 2) which was also reflected in their intergroup comparison (Table II). A significant increment was observed in final serum ALP levels (251 ± 17.61) of drug treated Group II (Fig 2). Comparison of G-II (M) with control group G-I revealed statistically significant difference (Table I). A trend of lowering of ALP levels was displayed by NAC pretreatment as

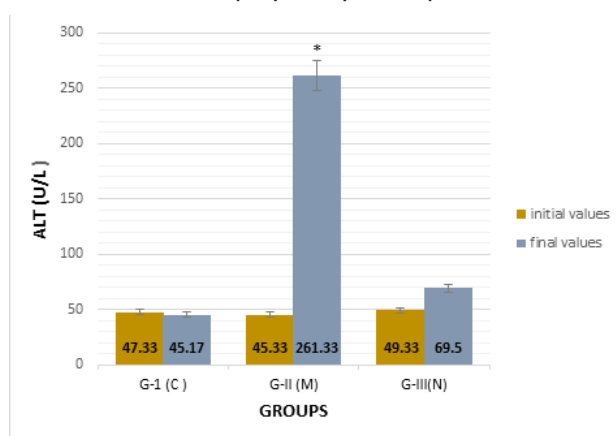


Fig 1: Initial and final values of ALT (U/L) of G-I, G-II and G-III * $p < 0.05$ =significant

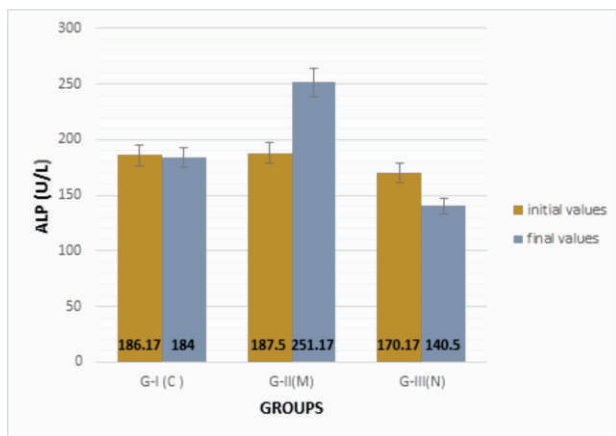


Fig 2: Initial and final values of ALP (U/L) of G-I, G-II and G-III * $p < 0.05$ = significant

Table I: Comparison of ALT and ALP between G-I and G-III

Parameter	Initial values (0 hour)		Final values (5 hours)	
	G-I	G-II	G-I	G-II
ALT (U/L)	47.33	45.33	45.17	261.33
SEM	9.87	9.84	10.03	20.30
<i>p</i> -value	0.98		0.00*	
ALP (U/L)	186.17	187.50	184.00	251.17
SEM	16.81	14.46	15.69	17.61
<i>p</i> -value	0.99		0.03*	

* p value < 0.05 = significant

Table II: Comparison of ALT and ALP between G-I and G-III

Parameter	Initial values (0 hour)		Final values (5 hours)	
	G-I	G-III	G-I	G-III
ALT(U/L)	47.33	49.33	45.17	69.50
SEM	9.87	7.24	10.03	6.13
<i>p</i> -value	0.98		0.43	
ALP(U/L)	186.17	170.17	184.00	140.50
SEM	16.81	14.75	15.69	13.50
<i>p</i> -value	0.74		0.21	

* p value < 0.05 = significant

Table III: Comparison of ALT and ALP between G-II and G-III

Parameter	Initial values (0 hour)		Final values (5 hours)	
	G-II	G-III	G-II	G-III
ALT(U/L)	45.33	49.33	261.33	69.50
SEM	9.84	7.24	20.30	6.13
<i>p</i> -value	0.94		0.00*	
ALP(U/L)	187.50	170.17	251.17	140.5
SEM	14.46	14.75	17.61	13.50
<i>p</i> -value	0.71		0.00*	

* p value < 0.05 = significant

evident by p value < 0.05 when compared with G-II (M) (Table III).

Histopathological Findings

Light microscopy of H & E stained slides of control group showed normal lobular appearance with central vein, portal triad and radiating hepatocyte cords (Fig 3). MMI administration caused cellular discontinuity, vascular congestion, loss of hepatocyte radial distribution and inflammatory cell infiltration (Fig 4 and 5). NAC pretreatment resulted

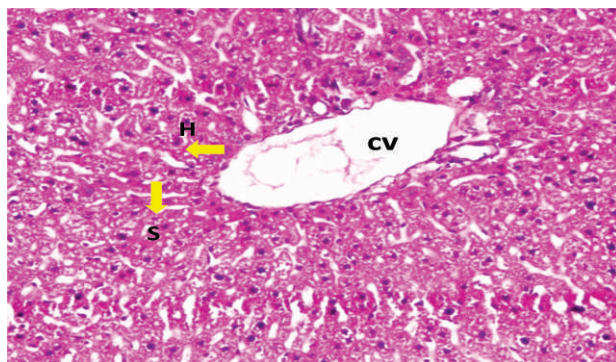


Fig 3: Pictograph of H & E stained liver specimen of control group at 40X showing central vein (CV), hepatocyte (H) and sinusoid space (S)

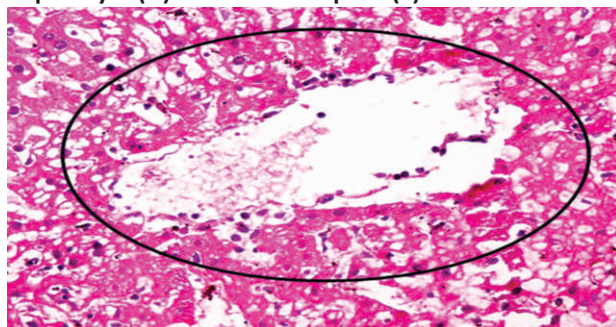


Fig 4: Pictograph of MMI treated group (M) AT 40X revealing cellular discontinuity and loss of radial distribution of hepatocytes.

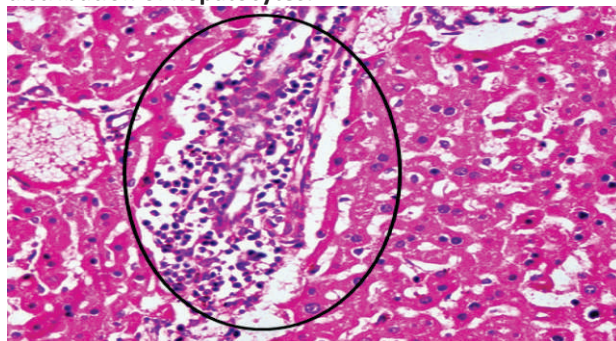


Fig 5: Pictograph of MMI treated group (M) AT 40X revealing portal inflammation

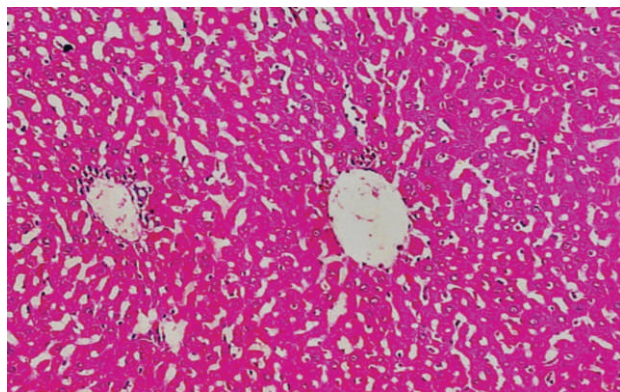


Fig 6: Pictograph of NAC treated group showing preserved architecture of hepatic parenchyma and portal triad with minimal inflammation
in preservation of liver architecture with minimal portal and lobular inflammation (Fig 6).

Discussion

Drug induced liver injury (DILI) is an unresolved health problem with an impact well beyond the number of cases occurring annually. It has become the most common reason for termination of drug development and withdrawal of approved products from market. Antithyroid medicines are included among the thousand (1000) drugs known to cause hepatic damage.¹⁵ Although the precise mechanism of MMI induced hepatotoxicity requires further exploration, however the role of reactive metabolite, oxidative and carbonyl stress, intracellular target dysfunction and immunological reaction has been implicated. The hepatotoxic metabolites produced as a result of biotransformation are capable of reacting with enzymatic and non-enzymatic antioxidants (GSH) rendering them ineffective and ensuing toxicity.¹⁶

Liver is central to all detoxification processes and adversely targeted by MMI during its administration. Our results showed that MMI produced an abnormal increase in ALT and ALP ($p < 0.05$) which was reflected as cellular discontinuity, necrosis and portal inflammation on microscopy. The significant rise in biochemical markers and histopathological findings were in accordance with the research of Tashkandi and his fellows in 2014.¹⁷ They demonstrated that administration of MMI produced a percentage increase of 202 and 191 in ALT and ALP along with 61% decrease in antioxidant enzymes. Coherent with our findings, Heidari and mates revealed elevation of liver enzymes with

concomitant decrease in GSH levels as a consequence of MMI induced hepatic insult.¹⁸ This highlights the role of oxidative stress in pathophysiology of MMI induced hepatic insult and the function of GSH in detoxification of its toxic intermediates. Thus GSH depleted hepatocytes are more susceptible to MMI induced injury producing remarkable damage at one thirtieth the normal toxic dose.⁹

Antioxidants have been documented to play their protective role in conditions set in the background of oxidative stress and impede progression of these diseases. Studies have revealed the hepatoprotective potential of many amino acids against drug induced liver injuries due to their antioxidant effects.⁶ Present study evaluated the protective capacity of N-acetylcysteine (NAC) in MMI induced hepatotoxicity. Pretreatment with acetylated cysteine in G-III (N-group) prevented the elevation of ALT and ALP observed in MMI treated group –II ($p < 0.00$). Injection of NAC one hour before MMI also managed to preserve the hepatic architecture with minimal inflammatory changes on histopathology. Insignificant difference ($p > 0.05$) between ALT and ALP of control group (C) and NAC pretreated group-III also adds weight to the hepatoprotective effect of NAC. Heidari and colleagues demonstrated that administration of organosulfur compounds attenuated cell death and prevented ROS formation, mitochondrial damage and lipid peroxidation caused by MMI.¹⁹

Since many studies has recognized oxidative stress as a major causative factor of MMI induced cellular damage^{4,16}, NAC's beneficial effects can be attributed to its direct and indirect antioxidant properties. Acting as membrane permeable source of L-cysteine for endogenous GSH, it can facilitate neutralization of cytotoxic metabolites before they can initiate damage.^{20,21} This acetylated amino acid can also defend against liver damage by scavenging free radicals and toxic aldehydes.²² This attenuation of oxidative stress through prevention of GSH depletion and glyoxal trapping by NAC was also reported by Heidari and mates.²³

The results affirmed the notion that NAC extends its protective effects against MMI induced liver damage evident by prevention of rise of serum ALT and ALP

along with preservation of hepatic lobular organization.

Conclusion

N-acetylcysteine holds hepatoprotective potential against MMI induced liver injury due to broad spectrum of physiological activities, however further investigation is required to endorse the prophylactic role of NAC in thionamide induced hepatotoxicity.

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ORIGINAL ARTICLE

Correlation between Nerve Conduction Studies and Neurological Scores According to Fibre Type in Patients with Diabetic Sensorimotor Polyneuropathy

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ABSTRACT

Objective: Purpose of this study was to determine association between nerve conduction studies and neurological examination scores in patients with diabetes who had known detectable sensorimotor neuropathy.

Study Design: Cross sectional descriptive study.

Place and Duration of Study: This study was conducted at the Islamic International Medical College, Combined Military Hospital and Armed Forces Institute of Rehabilitative Medicine in Rawalpindi, Pakistan, from January 2006 to January 2015.

Materials and Methods: Patients with confirmed diabetes (n=30) and clinically detectable sensorimotor polyneuropathy according to clinical scores were selected for inclusion. The type of fiber involved was determined on the basis of the modified Diabetic Neuropathy Symptom (DNS) score and modified Diabetic Neuropathy Examination (DNE) score.

Results: Neuropathy Disability Score results showed a significant positive correlation with the results of nerve conduction studies in both large and small types of fiber.

Conclusion: In patients with type 2 diabetes and advanced neuropathy, association among the results of Neuropathy Disability scores and nerve conduction studies indicates the impaired functioning of both small and large nerve fiber.

Key Words: Diabetes, Diabetic Neuropathy, Diabetes Mellitus.

Introduction

In 2014, the nationwide prevalence of diabetes mellitus was estimated at 6.8% in Pakistan.¹ Uncontrolled diabetes mellitus may lead to neuropathy, retinopathy and macrovascular disease. If these complications are left unchecked, then they may lead to blindness,² foot ulcers³ and sexual dysfunction.⁴ Diabetic neuropathy, one of the complications of diabetes, arises due to derangements in the levels of insulin and glucose.

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This results in abnormal flow in ion channels such as sodium potassium pumps, sodium channels or calcium channels, and these disruptions can cause abnormal nerve conduction.^{5,6,7}

The Diabetic Neuropathy Symptom (DNS) and Diabetic Neuropathy Examination (DNE) scores can be used to detect diabetic polyneuropathy.⁵ The clinical diagnosis can be confirmed by scoring systems such as the Neuropathy Disability Score (NDS) and Neuropathy Symptom Score (NSS). Hence, for our study DNS and DNE scores are used whereas, clinical diagnosis is confirmed by NDS and NSS.

Clinically, large-fiber neuropathies can be distinguished from small-fiber neuropathies during neurologic testing. If tendon reflexes or vibration sense are impaired, Aa or Ab fibers are involved,⁶ whereas if pain or thermal sensation are impaired, Ad or C fibers are involved. The American Academy of Neurology has suggested that a combination of clinical symptoms and signs with electrodiagnostic findings provides the most accurate diagnosis of distal symmetric polyneuropathy.⁷

In previous studies, a significant correlation was

found between clinical findings and neurophysiological test results depending on the fiber type. Unlike earlier studies, however, our approach included four known neurological scoring systems and compared their scores according to fiber type. The objective of this study was to search for correlations between the results of nerve conduction studies and neurological examination scores in clinically detectable sensorimotor neuropathy in patients with type 2 diabetes, according to the type of fibre involved.

Materials and Methods

This cross-sectional descriptive study was conducted from January 2006 to January 2015. Purposive sampling was used to select 30 patients diagnosed as having type 2 diabetes from outpatients who had clinically detectable peripheral neuropathy (n=30) on the basis of Diabetic Neuropathy Symptom (DNS) and Diabetic Neuropathy Examination (DNE) scores. The inclusion criteria were age between 25 and 61 years (male or female) and duration of known diabetes greater than 1 year. Patients with any other type of neuropathy or musculoskeletal disorder, and patients, who were taking medications that could affect the course of neuropathy, were excluded from the study.

Diabetic neuropathy was confirmed by history and by DNS and DNE scores. Neuropathy was graded on the basis of the modified Neuropathy Disability Score (NDS) and Neuropathy Symptom Score (NSS) results. Physical examination was done, including tendon reflexes and vibration sense. If tendon reflexes or vibration sense was impaired, the patient was considered to have large-fiber neuropathy; if pain or thermal sensation was impaired, the patient was considered to have small-fiber involvement. If both types of impairment were observed, the patient was considered to have both large- and small-fiber neuropathy.

A simplified protocol for nerve conduction studies was used to record amplitudes, velocities and latencies from a minimum of two and a maximum of six nerves. Amplitudes, velocities and latencies were measured individually, and were assigned numerical grades of severity according to their values. Then a net score was assigned to each variable, and each value was labeled as normal, mild, moderate, or severe neuropathy based on the average value

recorded from two to six nerves. The presence or absence of neuropathy was recorded as an outcome. An overall score (grade) of normal, mild, moderate or severe neuropathy was assigned to the results of nerve conduction studies on the basis of the recorded amplitudes, velocities and latencies. F wave and H reflex were tested only if needed distinguish between types of neuropathy.

Fasting and random blood glucose were measured by glucometer. Hemoglobin (HbA1c) was measured using High performance liquid chromatography (HPLC) in AFIP laboratory to check long-term blood glucose control. Means and standard deviations of fasting blood glucose, random blood glucose and HbA1c were calculated. Spearman's rho test was used to estimate the correlation between nerve conduction measures and neurological examination scores according to the fiber type. The data were analyzed with SPSS v.20.0 software.

Results

Each neurological score was compared to different components of nerve conduction studies in all 30 patients. The laboratory profile of the patients was fasting blood glucose (mmol/L) 9.05 ± 3.8 (mean \pm SD), random blood glucose (mmol/L) 13.49 ± 4.65 (mean \pm SD), and Hb A1c(%) 6.82 ± 1.36 (mean \pm SD). Correlations were calculated for neuropathies involving large fibers and both fiber types, but could not be calculated for small-fiber neuropathies because none of the patients in this study had exclusively small-fiber involvement. Among the 30 patients, both fiber types were involved in 12 (40%), large-fiber neuropathy was identified in 17 (56.7%), and the fiber type in 1 patient (3.3%) could not be determined.

Regardless of the type of fiber involved, NDS correlated with the findings of nerve conduction studies. The other scores, i.e. DNS, DNE and NSS, did not correlate significantly with components of nerve conduction studies regardless of whether small, large or both types of fiber were involved. Details of these results are shown in Table I.

The positive correlations between NDS scores and different components of nerve conduction studies are shown in Figures 1-4.

Table I: Correlation between neurological scores and nerve conduction studies according to type of fiber

12 out of 30					
Nerve conduction study variables	Value	DNS	NSS	NDS	DNE
Nerve conduction study scores	r	-0.058	-0.323	0.727	-0.046
	p	0.857	0.306	0.007**	0.886
Nerve score amplitudes	r	-0.058	-0.323	0.727	0.093
	p	0.857	0.306	0.007**	0.775
Nerve score velocities	r	0.266	-0.023	0.551	-0.018
	p	0.404	0.942	0.063	0.957
Nerve score latencies	r	0.122	-0.313	0.697	-0.048
	p	0.706	0.321	0.012*	0.881

*Correlation significant at the 0.05 level (2-tailed)

**Correlation significant at the 0.01level (2-tailed)

DNS: Diabetic Neuropathy Symptom score.

DNE: Diabetic Neuropathy Examination score.

NSS: Neuropathy Symptom Score.

NDS: Neuropathy Disability Score

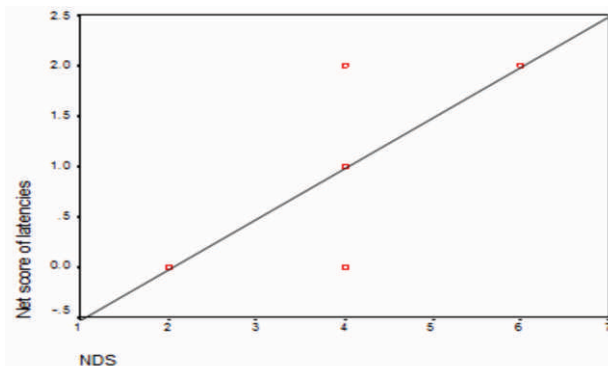


Fig 1: Correlation between Neuropathy Disability Score and net score of latencies found in nerve conduction studies (n=30) in persons with type 2 diabetes. Scatter plot showing significant positive correlation between Neuropathy Disability Score and latencies in nerve conduction studies in both types of fiber.

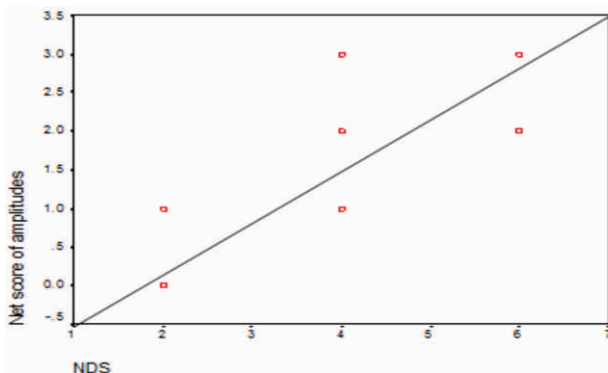


Fig 2: Correlation between Neuropathy Disability Score and net score of amplitudes found in nerve conduction studies (n=30) in persons with type 2 diabetes. Scatter plot showing significant positive correlation between Neuropathy Disability Score and amplitudes in nerve conduction studies in both types of fiber

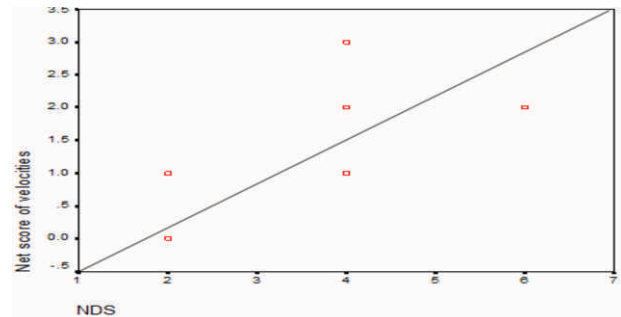


Fig 3: Correlation between Neuropathy Disability Score and net score of velocities found in nerve conduction studies (n=30) in persons with type 2 diabetes. Scatter plot showing nonsignificant positive correlation between Neuropathy Disability Score and velocities found in nerve conduction studies in both types of fiber.

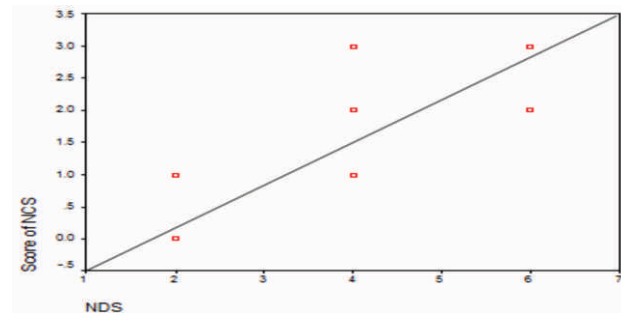


Fig 4: The correlation between Neuropathy Disability Score and score of nerve conduction studies (n=30) in persons with type 2 diabetes. Scatter plot showing significant positive correlation between Neuropathy Disability Score and in nerve conduction studies in both types of fiber

In patients with disorders affecting only large fiber, DNS, DNE, NSS and NDS results showed correlations with components of nerve conduction studies. These results are summarized in Table II.

Table II: Correlation between neurological scores and nerve conduction studies for large fiber type
Correlations were not significant.

17 out of 30					
Nerve conduction study variables	Value	DNS	NSS	NDS	DNE
Nerve conduction study scores	r	-0.225	0.085	0.229	0.169
	p	0.385	0.745	0.377	0.518
Nerve score amplitudes	r	-0.168	0.185	0.303	0.444
	p	0.519	0.476	0.237	0.074
Nerve score velocities	r	-0.139	0.146	0.147	0.050
	p	0.594	0.577	0.572	0.849
Nerve score latencies	r	-0.079	0.068	0.071	-0.051
	p	0.763	0.796	0.785	0.845

DNS: Diabetic Neuropathy Symptom score.

DNE: Diabetic Neuropathy Examination score

NSS: Neuropathy Symptom Score

NDS: Neuropathy Disability Score

Discussion

Our study shows a significant positive correlation between NDS and components of nerve conduction studies in patients with large- and small-fiber impairment. The clinical examination scoring systems we used were carefully selected to identify the type of fiber involved, and to allow the major components of neuropathy to be studied with straightforward clinical examination.⁸

Franssen et al. showed that amplitude in nerve conduction studies correlates with axonal neuropathy, which is highly predominant in our patients.⁹ Latency can also show significant correlation with axonal neuropathies, especially in advanced cases. Velocity, in contrast, was not affected much – an unsurprising lack of association with axonal neuropathies, as pointed out by Malik, et al.¹⁰ Although we found correlations between NDS scores and velocity in nerve conduction studies regardless of fiber type, this result may be due to advanced neuropathy in which demyelination has started in addition to axonal loss.

Feki et al. found a significant correlation between NDS results and nerve conduction findings, as well as between NSS and nerve conduction results, but they also found, as we did, that the former correlation was more significant.¹¹ Although 12 of our patients had deranged nerve conduction findings consistent with small-fiber disorders, their clinical scores reflected signs of both small- and large-fiber neuropathy; therefore, these patients were considered to have impairments in both types of fiber.

Lefaucheur et al. found a significant correlation between clinical findings and neurophysiological test results according to fiber type. These authors first determined the type of fiber involved on the basis of nerve conduction studies and clinical examination independently, and then looked for correlations.¹²

We determined which type of fiber was involved by clinical examination and then looked for correlations between the clinical examination results and nerve conduction studies according to fiber type. Unlike earlier studies, however, our approach included four known neurological scoring systems and compared their scores according to fiber type. Regarding NDS, we found that the scores correlated with nerve conduction findings, although this correlation was confirmed only in patients with neuropathy that

affected both types of fiber.

Liu et al. showed that the most common clinical and electrophysiological manifestation of diabetic neuropathy is a sensory disturbance, which is more severe in the lower limbs.¹³ However, when sensory symptoms are considered, electrophysiological changes are not always consistent with clinical manifestations.¹⁴

Symptom scores are not always reliable because they focus on symptoms alone. The exploration of symptoms is always patient-dependent and is affected by many confounding factors such as the patient's mental state, literacy level and attitude toward being labeled neuropathic or not. Symptom scores are thus unreliable when used alone to assess neuropathy, at least in the examination protocols currently in use. In many neuropathies, the pathophysiological and clinical profiles may be heterogeneous across patients.¹⁵ This variability may be responsible for the differences in results when patients are examined with two or more different techniques, as each technique focuses on a specific aspect of the patient's illness.

Our impression is that if a more comprehensive battery of symptoms were used to assess neuropathy, the results may be more reliable. Searching for correlations between the findings from neurological examination and nerve conduction studies is a way to explore two different aspects of neuropathy. Nerve conduction studies measure the strength of local signal transport, whereas neurological examination assesses the overall function of the nerve as well as the muscles involved. However, abnormal findings in nerve conduction studies also eventually point to impaired overall nerve functioning. We found that in patients with both small and large fiber involvement, the correlation between these two sources of information was indicative of more advanced neuropathy.

If carefully examined and investigated, many idiopathic neuropathies can be assigned to known causes of neuropathy after appropriate testing.¹⁶ The findings of patient assessment by clinical examination also depend on normal receptor functioning, which is not the case with nerve conduction studies.

Rota et al. correlated clinical neuropathy with the

results of electrophysiological tests, but did not categorize patients according to severity.¹⁷ They investigated only persons with impaired neurological scores according to the NDS and NSS, and who also had impaired nerve conduction. Their results are consistent with our findings. In the present study we also recorded nerve conduction in those patients who did not have positive findings on clinical examination, and found neuropathy in many of these patients. This aspect of our study is important in establishing the value of nerve conduction studies in patients like the ones enrolled in our study.

An important difference between our study and others is that usually a full battery of NDS and NSS is claimed to have been tested, which is rather impractical in daily clinical practice both for the physician and for outpatients, especially in settings with a heavy patient turnover.^{18,19} A complete battery of scoring systems assesses many components which are not related to peripheral neuropathy, and so are not relevant to the aims of the present study. We have, however, included modified forms of both examination systems, with the aim of testing related components of nerve functioning in an effort to search for an approach to clinical diagnosis that would be practical for the physician.

In Pakistan it is common practice to perform neurological examination and nerve conduction studies in centers where both facilities are available. To date, however, the correlations between these two methods have not been analyzed either directly (in comparison to clinical examination findings) or according to the type of fiber involved.

In our sample we are unable to confirm significant correlations between clinical signs of neuropathy documented with different scoring systems and evidence of impaired nerve functioning obtained with nerve conduction studies in patients with small-fiber dysfunction, but the correlations are significant in those with large-fiber or mixed large- and small-fiber dysfunction. Our findings give us insight into the reasons for differences in the performance of various scoring systems used to detect neuropathy. However, the influence of confounding factors such as the subjectivity of clinical assessments needs to be taken into account. Future studies should include more specific variables. Moreover, many patients do not recognize their symptoms unless asked about

them through direct questioning. This aspect may also contribute to discrepancies between the results of sensory clinical scoring systems and nerve conduction studies among patients with diabetic sensorimotor polyneuropathy involving different types of nerve fibers.

According to our results, more patients had large- or mixed-fiber impairment rather than only small-fiber impairment. This finding needs to be investigated further in patients with newly-diagnosed diabetes to determine whether small or large fibers are initially affected, and follow-up studies will be needed to determine whether impairment in one type of fiber evolves toward impairment in the other type. It is also possible that small fibers, if affected early, may recover earlier during treatment for hyperglycemia, whereas mainly large fiber impairment appears later, or remains detectable for longer during the course of diabetes.

Conclusion

In patients with type 2 diabetes and advanced neuropathy, our use of more objective examination tools showed that the correlation between the findings of nerve conduction studies and neurological examination scores indicative of sensorimotor neuropathy reflects the involvement of a specific type of nerve fiber. For patients with both small- and large-fiber neuropathy, objective tests such as the NDS also correlate with nerve conduction study results.

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ORIGINAL ARTICLE

Perceptions of Dental Students Studying at Ras Al Khaimah College of Dental Sciences to Their Educational Environment Using the Dundee Ready Educational Environment Measure –DREEM

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ABSTRACT

Objective: To measure the perceptions of the dental students studying in Ras al Khaimah College of Dental Sciences regarding the educational environment using the DREEM questionnaire.

Study Design: Cross sectional descriptive study.

Place and Duration of Study: The study was conducted at Ras al Khaimah College of Dental Sciences from 15th of November 2015 to the 1st of March 2016.

Materials and Methods: The study was conducted on dental students of Ras Al Khaimah College of Dental Sciences (RAKCODS) from first till fifth year. DREEM questionnaires were distributed to a total of 320 students out of which 245 students returned filled up questionnaires which were collected at the end of the week. DREEM questionnaire comprises of a set of 50 questions which are graded on a likert scale of 0-4 by students. All the data was tabulated in SPSS 16.0 and the results were compared against the fixed values given in original DREEM inventory.

Results: Out of n=320 students, 245 responded which gave us a response rate of 76.5%. Of all the participants, 94 (38%) were male students and 151 (62%) were female students. The total mean scores for the five major categories, namely, Student's perceptions of learning (SPL), Student perceptions of teachers (SPT), Students' academic self-preparation (SAP), Students' perception of atmosphere (SPA), and Students' self-perception (SSP), in the respective order, were 31.08/48, 28.15/44, 21.03/32, 29.87/48, 16.65/28. The global score was 126.78 out of 200 which indicates the students find the educational environment of RAKCODS more positive than negative.

Conclusion: This study indicates that students find the dental environment provided within RAKCODS more positive than negative. High scores have been identified in student's perception of learning and the faculty. Low scores have been attributed to the teaching methodology particularly teacher centered learning.

Key Words: Dentistry, Dental Students, DREEM, Educational Environment, RAKCODS.

Introduction

The educational environment comprises of physical and psychological that tends to happen in a classroom, faculty, department and the institution. The environment provided within any institute, be it, medicine or dentistry, is vital in determining the success or failure of any institute.¹ As the times are changing, so is the teacher's role from being an educator to being a guide in helping students to learn

new experiences.² An established correlation has been stated between an educational environment provided to a student and its impact on the students' achievement, satisfaction and success.³ For this reason, it is the responsibility of all dental and medical educators, in all dental or medical institutions, to make sure that all dentists are being trained in an environment that is supportive yet challenging in a healthy way so as to promote learning.⁴ The educational environment is considered as one of the areas that should be addressed while evaluating any medical or dental program within an institute, by the world federation for medical education.⁵

In order to make improvements within the curriculum of any educational institution, the understanding of its education environment is very important to determine the strengths and weaknesses within that institution, in order to enhance student's learning. In order to do so, Roff et

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al developed a useful tool at Dundee University UK, "Dundee Ready Education Environment Measure (DREEM).⁶ It is a validated tool and highly reliable which can be used for multiple purposes such as comparative analysis between students' perceptions of an educational climate within any institution.⁷

The DREEM questionnaire consists of fifty questions subdivided into 5 sub-domains, with a total global score of 200. Because of its high reliability and validity, it has been tested on student's populations in Pakistan, India, UK, Malaysia, Greece, Saudi Arabia, Bangladesh, Thailand, Ethiopia, Argentina and many other countries.⁸

Ras Al Khaimah College of Dental Sciences (RAKCDS) was built in the year 2007 in Ras al Khaimah, United Arab Emirates. It consists of a vast diversity of students from different countries. There is a lot of effort done by the institution to provide the highest standard of education and to provide them with the suitable environment that helps and motivates them to build their clinical and interactive skills, which are very important in the dental field. For this reason, the study was conducted in order to understand the student's perceptions of the educational environment provided within RAKCDS, so as to bring a positive change, if needed, for the benefit of the dental students.

Materials and Methods

A cross sectional descriptive study was conducted at Ras Al Khaimah College of dental sciences within a span of 3 months from 15th November 2015 to 1st March 2016. All the students studying in Ras al Khaimah College of Dental Sciences were included in the study. Student who did not consent to participate in study or incompletely filled questionnaires were automatically excluded from study.

The duration of dental program is five years followed by one year of internship, in first 3 years students are taught preclinical subjects, and in last two years they are taught the clinical subjects. The students within the college are exposed to the clinical environment from their first year for clinical observation rounds to familiarize them with the clinical environment by the time they start their clinical training in the third year. The DREEM questionnaires were distributed in each class, to a total of 320 students. Before the questionnaires were distributed, the aim of the

research was explained to the students and clear instructions were given to them regarding the data collection process, this was followed by their consent. The questionnaires were collected from the participating students after a week, by the co-investigators.

The DREEM questionnaire principally comprises of fifty questions subdivided into five main categories; (1) Student's perceptions of learning (SPL), (2) Student perceptions of teachers (SPT), (3) Students' academic self preparation (SAP), (4) Students' perception of atmosphere (SPA), and (5) Students' self perception (SSP). All of these categories contain corresponding questions which were measured using the Likert scale 0-4 where 0 stands for strongly disagree, 1 for disagree, 2 for unsure, 3 for agree and 4 for strongly agree. The Likert scale is used to evaluate all the questions except nine questions (4, 8, 9, 17, 25, 35, 39, 48 and 50) which are negative statements and, are analyzed in a reverse score such as, 0 for strongly agree, 1 for agree, 2 for unsure, 3 for disagree, and 4 for strongly disagree.

The maximum score within each sub category depending upon the number of questions each category, are, category 1 (SPL) contains 12 questions giving the maximum score of 48 (12x4), category 2 (SPT) contains 11 questions giving the maximum score of 44 (11x4), category 3 (SAP) contains 8 questions giving the maximum score of 32 (8x4), category 4 (SPA) contains 12 questions giving the maximum score of 48 (12x4), category 5 (SSP) contains 7 questions giving the maximum score of 28 (7x4). The total global score of DREEM questionnaire is 200 encompassing all the sub-categories.

The scores were interpreted according to the following criteria, for each subscale; Category 1 (SPL)- 0-12 means very poor, 13-24 means teaching is viewed negatively, 25-36 means a more positive perception, 37-48 means teaching is highly thought of. Category 2 (SPT)- 0-11 means Abysmal, 12-22 means in need of some retraining, 23-33 means moving in the right direction, 34-44 means model teachers. Category 3 (SAP)- 0-11 means Abysmal, 12-22 means in need of some retraining, 23-33 means moving in the right direction, 34-44 means model teachers. Category 4 (SPA)- 0-12 means a terrible environment, 13-24 means there are many issues that need changing, 25-36 means a more positive

attitude, 37-48 means a good feeling overall. Category 5 (SSP)- 0-7 means miserable, 8-14 means not a nice place, 15-21 means not too bad, 22-28 means very good socially. For the interpretation of global DREEM score, 0-50 means very poor, 51-100 means plenty of problems, 101-150 means more positive than negative, 151-200 means excellent. Scores of individual questions determined a more specific response to the educational environment. Questions with a mean score of 2 and below, with the exception of negative questions, were considered problem areas that required more attention. Questions with a mean score between 2 and 3 were considered neither weak nor strong, but could be further improved. Mean scores of 3 and above were considered as positive points whereas, a mean score of 3.5 or above, for any question, were considered as the real positive points. Similarly, for negative questions, any mean score of 2 and above indicates problem areas which require attention. The Global DREEM score of 200 indicates an ideal educational environment.

All the data collected from the questionnaires were analyzed using SPSS 22.0 and Microsoft Excel. Mean scores were calculated for every individual item, sub-categories and finally the DREEM total score.

Results

Out of 320 students, only 245 filled the questionnaires and returned them, which gave us a response rate of 76.5%. Of all the participants, 94 (38%) were male students and 151 (62%) were female students.

Table I indicates the total mean scores for the five major categories, namely, Students' perceptions of learning (SPL), Students' perceptions of teachers (SPT), Students' academic self preparation (SAP), Students' perception of atmosphere (SPA), and Students' self perception (SSP), in the respective order, are 31.08/48, 28.15/44, 21.03/32, 29.87/48, 16.65/28. The table also gives mean values based on gender, where male students are rated higher than female students by a very little margin. The total DREEM score was 126.78/200.

Table II shows the mean values for each individual question with respect to gender of the students. Only 1 question, "The teachers are knowledgeable", had a score >3 which indicates a real positive point, majority of the questions had the score above 2,

Table I: Total mean scores of the responses within each sub category along with their interpretation

Sub Categories	Max Score	Mean as per Gender of Participant		Total Mean	Interpretation
		Male	Female		
Students' perceptions of learning	48	31.19	31	31.08	A more positive perception
Students' perceptions of teachers	44	28.25	28.08	28.15	Moving in the right direction
Students' academic self preparation	32	21.13	21	21.03	Feeling more on the positive side
Students' perception of atmosphere	48	30.43	29.53	29.87	A more positive attitude
Students' self perception	28	17.11	16.37	16.65	Not too bad
Total DREEM Score	200	-	-	126.78	More positive than negative

which indicates neutrality, but a little improvement would help. Amongst negative questions, "The teaching overemphasizes factual learning", "The teaching is too teacher-centered", "The teachers are authoritarian", "The students irritate the teachers", "Cheating is a problem in this school " had scores >2, which means this is a problematic area that requires attention.

Discussion

For the assessment of the educational environment, feedback by the students is important. Between the two groups, the ratio of female participants to male participants is higher, considering, the total number of female students are higher in number than male students within university.

The overall DREEM score was 126.78 out of 200 which indicates the students find the curriculum within RAKCODS more positive than negative. Although the differences between the mean values of male and female participants is barely minimum, however, the mean values of male students (128.11) are a bit higher than female students (125.98).

The overall response of the students to sub category 'Students' perceptions of learning' were 31.08 out of a total score of 48 indicating a more positive perception of the learning environment attained within the institution, which means the students find

the teaching experience interesting, focused and motivates them to be a good learner.

The response of students to 'students' perception of teachers' was 28.15/44 indicating the students find the teachers moving in the right direction when it comes to teaching them. Questions such as 'The teachers are knowledgeable' (Table II, question 2) have a mean score of 3.11 which is a real positive point. Questions like 'The teachers have good communications skills with patients' (Table II question 18), 'The teachers give clear examples' (Table II, question 37), 'The teachers are well prepared for their classes' (Table III, question 40) have high mean values, 2.77, 2.74, 2.86, in respective order, which means the students find the teachers having good communication skills with both the students in class and with patients in clinics and both of these factors are important for effective diagnosis, management and treatment of patients and to attain a comfortable relation with the patient which automatically aids them in trusting the students as a doctor in clinical years and, therefore, be compliant. This also indicates the students find the teachers well prepared for the class. It should be noted, being able to communicate with patients is quite fundamental for any dentist. Since the students are exposed to the clinical environment from the first year, being able to observe the teachers within the clinical environment proves to be a good role model to them in developing attitudes and morality to treat patients.

The overall response rate of students to academic self-preparation was 21.08 out of 32 which indicates students find the curriculum more towards the positive side. The response of the students to atmosphere and self-perception, respectively, were 29.87 out of 48, 16.65 out of 28 indicating a high score. Students find the educational environment within the institute quite positive and their social perception isn't too bad either. A very high mean score was observed for 'have good friends in this school' (Table 3, question 15) and 'My social life is good' (Table III, question 19) which means the students are comfortable within the university, are able to bond well which indicates generally a good and friendly environment.

The response rate of students to negative statements were generally favorable except questions like 'The teaching overemphasizes factual learning' (Table III,

question 25), 'The teachers are authoritarian' (Table II, question 9, 'The students irritate the teachers' (Table II, question 50), 'Cheating is a problem in this school' (Table II, question 17), teaching is too teacher centered, (Table II, question 48) which had a high mean score, in respective order, 2.56, 2.29, 2.34, 2.19, 2.13. These scores indicate a problem area which requires attention.

The overall DREEM score of the students with respect to the curriculum offered in Ras al Khaimah college of Dental Sciences, shows a higher score if we compare our values with international universities, such as, medical and dental schools in Sri Lanka, Nigeria, Pakistan and India which were 108⁸, 118⁹, 114.4¹⁰ and 124¹¹ respectively. The score of UK medical schools (139) is a bit higher than our score.¹² All of these studies provide a comparative analysis of our university with the internationally recognized institutions.

The important questions raised from the results are that there are many reasons which can render a student from irritating a teacher such as if they find the professor disorganized with their lecture, or not interacting with them, starting a class early and ending it late, teaching directly from their notes or board, not being innovative during teaching session, never grading the assessment papers or assigned work on time. Creating a positive environment is a matter of great concern for all the teachers.¹³ Being authoritative towards students in order to facilitate learning will never make the students interested enough to do that on their own. The teaching sessions should be stimulating, organized and innovative on daily basis as the teachers being in a dental profession are more of cultivator's proper human relationships and how to induce a good morality.¹⁴ We must always remember, a good teacher is one who knows where to begin, what to include and omit, know the stages that motivate students to master the subject.¹⁵

The main limitation we had in the study was the students who did not fill out or complete the questionnaires, because of which the students were explained the logic behind each and every question and a week's time was given to them in order to obtain accurate results.

The concept of factual learning is not really induced within the institution as much as it is adapted by the

students to find an easy way out for their exams. For this reason, all the lectures should be precisely centered on guiding the students on what aspects of a particular subject they should focus on, and the sessions should be based on problem based learning which lets the students to collectively brainstorm their way to a dental solution. With these questions we still cannot identify what aspects of the teacher's mannerism end up making the students to irritate them, which again, will require a more detailed study.

Table II: Mean dream results of each question within sub category, along with gender and mean score

Item	Questions corresponding to main category	Mean Values		
		Male	Female	Total Mean
	1. Students' perceptions of learning:			
1	I am encouraged to participate in class	2.64	2.67	2.66
7	The teaching is often stimulating	2.59	2.64	2.62
13	The teaching is student-centered	2.67	2.50	2,57
16	The teaching is sufficiently concerned to develop my competence	2.78	2.62	2.68
20	The teaching is well focused	2.74	2.63	2.67
22	The teaching is sufficiently concerned to develop my confidence	2.38	2.42	2.40
24*	The teaching time is put to good use	2.67	2.85	2.78
25	The teaching overemphasizes factual learning	2.56	2.56	2.56
38	I am clear about the learning objectives of the course	2.85	2.78	2.81
44	The teaching encourages me to be an active learner	2.69	2.85	2.79
47	Long term learning is emphasized over the short term	2.44	2.39	2.41
48*	The teaching is too teacher-centered	2.18	2.09	2.13
	II. Students' perceptions of teachers:			
2	The teachers are knowledgeable	3.10	3.11	3.11

6	The teachers are tolerant	2.89	2.81	2.84
8*	The teachers ridicule at the students	2.11	1.83	1.93
9*	The teachers are authoritarian	2.41	2.22	2.29
18	The teachers have good communications skills with patients	2.72	2.79	2.77
29	The teachers are good at providing feedback to students	2.70	2.85	2.80
32	The teachers provide constructive criticism	2.59	2.50	2.53
37	The teachers give clear examples	2.71	2.76	2.74
39	The teachers get angry in class	1.86	1.99	1.94
40	The teachers are well prepared for their classes	2.79	2.91	2.86
50	The students irritate the teachers	2.38	2.31	2.34
III. Students' academic self-perceptions:				
5	Learning strategies which worked for me before continue to work for me	2.50	2.52	2.51
10	I am confident about passing this year	2.93	2.81	2.85
21	I feel I am being well prepared for my profession	2.61	2.84	2.75
26*	Last year's work has been good preparation for this year's work	2.23	2.45	2.37
27	I am able to memorize all I need	2.55	2.50	2.52
31*	I have learned a lot about empathy in my profession	2.63	2.59	2.60
41	My problem-solving skills are being well developed here	2.85	2.52	2.64
45	Much of what I have to learn seems relevant to a career in Dentistry.	2.83	2.77	2.79
IV. Students' perceptions of atmosphere:				
11	The atmosphere is relaxed during the ward teaching	2.60	2.60	2.60
12	This school is well timetabled	2.47	2.55	2.52
17	Cheating is a problem in this school	2.02	2.30	2.19

23	The atmosphere is relaxed during lectures	2.68	2.67	2.67
30	There are opportunities for me to develop interpersonal skills	2.71	2.63	2.66
33	I feel comfortable in class socially	2.86	2.67	2.74
34	The atmosphere is relaxed during seminars/tutorials	2.57	2.60	2.59
35	I find the experience disappointing	1.79	1.52	1.62
36	I am able to concentrate well	2.68	2.66	2.67
42	The enjoyment outweighs the stress of studying Dentistry.	2.47	2.34	2.39
43	The atmosphere motivates me as a learner	2.72	2.42	2.54
49	I feel able to ask the questions I want	2.86	2.57	2.68
V. Students' social self-perceptions:				
3	There is a good support system for students who get stressed	2.22	1.99	2.08
4	I am too tired to enjoy this course	1.93	1.90	1.91
14	I am rarely bored on the courses	2.09	1.99	2.02
15*	I have good friends in this school	3.15	2.88	2.98
19	My social life is good	2.97	2.83	2.89
28	I seldom feel lonely	1.98	2.04	2.02
46	My accommodation is pleasant	2.77	2.74	2.75

Efforts should be made by the teachers to shift the teaching from teacher centered to more of a student centered, encouraging them to be active learners. Once the students enter into a clinical environment, a more mature, complex and integrated approach should be employed to facilitate effective learning and these sessions should be innovative and targeting each student.

The strategies employed by SPICE model should be incorporated by all the medical and dental facilitators, which states that teaching should be innovative and based on community problems encountered on daily basis.¹⁶ This allows for a more systematic and organized approach which aids in active learning by students and, at the same time, shifts the focus of the pattern of education from

teacher to student.

FAIR principles further states that the teaching methods employed by facilitators may include any activity that is relevant to the student's educational system and allows an active participation from every individual.¹⁷ This will give a feedback to student to assess their own knowledge and improve themselves in the areas they lack.

In order to minimize the occurrence of cheating, exam methods should be conducive and innovative. Various strategies should be used such as computer based exam system; increase the number of invigilators and more than one assessment methods can be used to ensure students are not given an opportunity to cheat. Examination should be valid and reliable with more emphasis on OSCE's especially in clinical subjects

Apart from this, faculty development and training is also very important and this can be implemented by the teachers by keeping themselves upto date with the highest standards of teaching methods which are used internationally by attending the seminars and workshops on medical education annually.

Conclusion

The overall results obtained from the students of RAKCODS indicates, the environment attained by students is more positive than negative. Factors such as cheating, emphasis on factual learning, teachers being authoritarian, students irritating teachers, are all factors that require attention. Also, a better support system from the staff and the peers will improve the intellectual development of the students; so that they are able overcome their insecurities, and actively participate in problem based active learning. A collective change in the attitude and approach is imperative to enthuse a positive environment for these young minds, in order to mold them into a professional and competitive dental professionals.

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CASE REPORT

Early Diagnosis and Prompt Treatment – An Approach to Hamper Swine Flu Outbreak

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ABSTRACT

Swine flu is an acute respiratory disease also referred as novel A/H1N1, caused by influenza type A virus. Although currently in post pandemic phase, swine flu is considered as a major emerging disease and in this situation notification of every case is essential to interrupt transmission of disease. Therefore, we are reporting this case of 35 year male presented with one week history of sore throat, fever and constitutional symptoms, investigated for swine flu, and successfully treated with an excellent outcome.

Key Words: *Respiratory Disease, H1N1Inflenza, Swine Flu.*

Introduction

Swine flu is an acute respiratory disease caused by a relatively new strain of influenza virus A/H1N1.¹ In June 2009, pandemic of A/H1N1 flu spread in more than two continents, almost 375,000 laboratory confirmed cases and thousands of deaths reported to WHO in nearly 214 countries.² The first global estimates by CDC-Led Collaboration showed an estimated range of deaths between 151,700 and 575,400 people who perished worldwide from 2009 H1N1 virus infection during the first year the virus circulated. These global estimates were more than 15 times higher than the number of laboratory confirmed cases and deaths reported to the WHO.³ Consequently, localized epidemics are thought to be expected and considerable efforts are required to deal with this global threat.³

Pandemic (H1N1) 2009 is an influenza A virus belongs to family Orthomyxoviridae.⁴ The major virus component determining epidemiologic dynamics is HA antigen, which serves as the hemagglutinin attachment protein to enable binding and infecting cells.⁴ Influenza viruses are highly resilient in the environment, low temperature and low humidity favor aerosol transmission, explaining seasonal variation in temperate climates.⁴ Influenza viruses

have been isolated from many hosts including human beings, birds (chicken and ducks), pigs, horses etc. In humans, any preexisting chronic condition, cigarette smoking and alcohol consumption correlate with enhanced influenza virus-associated morbidity and mortality.⁴ The signs and symptoms of swine flu in humans are similar to seasonal influenza and characterized by fever, cough, sore throat, headache, malaise, muscle pain, nasal congestion, chills and fatigue.⁵ The high risk patients include children, elderly, pregnant women, people with chronic conditions and immunosuppressed.⁵

The ministry of health confirmed first swine flu case in Pakistan on August 10, 2009, the only source of virus being migrant people from abroad.⁶ There has been an increase in the number of swine flu cases and consequential deaths in various parts of Punjab and federal capital.⁶ During 2014, swine flu outbreak was observed in Multan, Khanewal, Taunsa, and Dera Ghazi Khan districts of Southern Punjab from where more than 10 cases of swine flu and five mortalities were reported.⁶ We are lacking medical, technical and diagnostic facilities and reporting of even a few cases in this situation is really alarming and needs attention.⁶

We present a case of swine flu successfully treated in our hospital.

Case Report

A 35 year male patient, accountant by profession, admitted with the complaints of sore throat and high grade fever with chills, rigors and cough, initially dry and later on productive for the last one week. He gave history of few episodes of sweating and palpitations. There was no other urinary or bowel

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complaint. He was a non-smoker, non-addict and gave family history of diabetes and ischemic heart disease. On general physical examination he had raised pulse rate and a temperature of 102°F. The examination of respiratory system revealed bilateral coarse crepitations all over the chest. Cardiac and other systemic examinations were within normal limit.

Complete blood count revealed total leukocyte count – $4 \times 10^9/l$, hemoglobin – 14.3 g/dl and platelet count – $193 \times 10^9/l$. ESR, liver function tests, serum electrolytes, renal function tests, random blood glucose and trop-T were normal. Urine analysis was also within normal limits. MP smear, blood culture, dengue serology NS-1, typhidot were all negative. O₂ saturation was 80 to 85% at room air without oxygen. Arterial Blood Gases showed hypoxia. The patient was put on anti malarial drugs and broad spectrum antibiotics. He responded well and became afebrile initially, later on developed dyspnoea and generalized body weakness. Chest X-ray was done showing bilateral lung infiltration in mid lung zone, suggestive of small airway inflammatory disease. ECG was also done which showed serial non specific T-wave inversion in chest leads. No abnormality was detected on echocardiography with normal ejection fraction.

A probable diagnosis of pneumonia (typical, atypical and viral) was made. The nasopharyngeal swab was sent for H₁N₁ serology to National Institute of Health to rule out viral pneumonia (swine flu) and the report was awaited. In the meanwhile he was put on broad spectrum antibiotics and antiviral treatment (Tamiflu 150 mg bd). Daily complete blood count reports showed platelet count dropped to $80 \times 10^9/l$ and TLC dropped to $2 \times 10^9/l$. Serum CK and LDH were markedly raised suggestive of viral pneumonias. D-dimers was negative (<200) and pulmonary embolism was ruled out. C-reactive proteins were mildly raised. Computed tomography of chest showed bilateral infiltrates in both lung fields and spirometry revealed severe restrictive lung disease. The patient was given intravenous steroids to treat acute interstitial pneumonia. After 5 days the report arrived which was positive for H₁N₁, intravenous steroids discontinued thereafter and antibiotics along with antiviral treatment was continued for 7 days. The patient was isolated and strict barrier

nursing was observed. The patient started to recover with gradual improvement of symptoms. All the investigations were repeated and were within normal limits, ECG changes reverted back to normal, chest x-ray showed decreased haziness and O₂ saturation increased. The patient was retained in the hospital for 10 days, his condition improved markedly. The case was notified to WHO and Ministry of health. The EDO Health's surveillance team visited the hospital and the patient to collect the epidemiological data and confirmation of the findings. The antiviral treatment (Tamiflu tablets) was provided by them and the entire team appreciated early diagnosis and prompt treatment of the case.

Discussion

The clinical continuum of the novel swine influenza infection is both self limited illness and in severe outcomes it can lead to respiratory failure and death similar to that seen among persons infected with earlier strains of swine origin influenza viruses and seasonal influenza viruses.⁵ The modes of transmission of influenza viruses in humans including swine influenza are mainly through the dissemination of large droplets and droplet nuclei expelled during coughing and sneezing of an infected person.⁶ There is also potential for transmission through direct contact with the patient and through contaminated fomites. In humans, it is most contagious during the first 5 days of the illness and can remain contagious for up to 10 days.^{5,6} Recommendations to prevent spread of the virus among humans include using standard infection control against influenza including frequent hand washing and use of mask, especially after being out in public. Anyone with flu-like symptoms such as a sudden fever, cough, or muscle aches should be isolated, contact a doctor to be tested and must not socialize.⁶ It has been recommended that patients with confirmed or suspected swine influenza infection should be placed in strict isolation and health care workers providing direct care for patients should observe strict barrier nursing precautions.⁷ After patient report to the health care setup, prompt sample collection and quick diagnosis help to reduce case fatality rate.⁸

During pandemics, health authorities may be uncertain about the spread and severity of the

disease and the effectiveness and safety of available interventions. This was the case during the swine flu (H1N1) pandemic of 2009–2010.⁸ During an infectious disease outbreak, it is crucial to be trained about the concerns, knowledge, attitudes, and behavior of the community to improve communication efforts by public health officials and clinicians.^{8,9} A great concern did not transform into higher conformity with precautionary recommendations, possibly due to the low level of knowledge about the disease among general public.⁹ Therefore, it is imperative to create awareness about mode of spread, preventive measures, availability of vaccines and effective medical treatment to prevent the disease transmission.^{10,11}

During the global H1N1 influenza A pandemic 2009–2010, swine flu vaccines were expeditiously licensed and a mass vaccination program for high risk groups was introduced in UK.¹² The rapid development of H1N1 vaccines to prevent further morbidity and mortality became public health priority and the first vaccines were licensed in October 2009.^{12,13} A mass vaccination program for high risk groups was launched in UK from October 2009 onwards and no significant safety issues were identified.¹³ The groups recommended to receive H1N1 influenza vaccine include; pregnant women, household contacts and caregivers for children younger than 6 months, healthcare and emergency medical services personnel, all people from 6 months through 24 years of age and persons aged 25 through 64 years who have health conditions associated with higher risk of medical complications from influenza.¹³

Although swine flu is currently in its post pandemic phase, there is always a risk of re-emergence of disease in susceptible population and localized outbreaks of varying scale with significant level of H1N1 transmission are expected.¹⁴ Understanding the perceptions of people and their potential resources to infectious disease threats would assist health officials to develop measures to respond this situation.¹⁴

The effectively treated case of swine flu described here implies the fact that the physicians must consider swine influenza infection in the differential diagnosis of patients with acute febrile respiratory illness for delivering good quality management and

treatment. The collaborative efforts of physicians, public health agencies and community education can facilitate to tackle this disease which has now become an emergent global menace.

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CASE REPORT

Acute Myeloid Leukaemia with PlasmacytosisYasmin Akhtar¹, Saqib Qayyum Ahmad², Shahid Jamal³**ABSTRACT**

Association of acute myeloid leukaemia with bone marrow plasmacytosis is a rare phenomenon with diverse underlying pathogenetic mechanisms. We report a case of a 75 years old diabetic male diagnosed as suffering with plasmacytosis. There were no lytic bone lesions or Bence-Jones proteinuria. Serum protein electrophoresis did not show a monoclonal band. A presumptive diagnosis of AML with reactive plasmacytosis was made. Possible conditions which can be considered in differential diagnosis are discussed.

Key Words: *Acute Myeloid Leukaemia, Multiple Myeloma, Reactive Plasmacytosis.*

Introduction

Association of acute myeloid leukaemia (AML) with bone marrow (BM) plasmacytosis is a rare phenomenon with only a few cases reported in the literature.¹ The underlying pathogenetic mechanisms causing BM plasmacytosis in patients of AML appear to be diverse as shown in the table. In the literature it has been mainly reported to occur in patients of AML as reactive proliferation discovered at the time of diagnosis; after induction-chemotherapy and rarely with simultaneous occurrence of multiple myeloma (MM).²⁻⁴ We report a case of AML with reactive plasmacytosis in an elderly diabetic and discuss the differential diagnosis.

Case Report

A 75-year-old male patient presented with complaints of low grade fever and lassitude of two month duration in the Medical OPD of Military Hospital Rawalpindi. He was a known case of type 2 diabetes mellitus for the past 25 years. On examination, he was pale and emaciated. Blood counts revealed pancytopenia with hemoglobin of 6.7 g/dl, white blood cell count of 1.8×10^9 /l and platelet count of 87×10^9 /l. Peripheral film showed rouleaux formation and ESR was 130 mm at the end of first hour. Serum urea and creatinine levels were raised (15.8 mmol/l and 225 μ mol/l respectively). Serum calcium levels were normal. His BM aspirate

showed 75% blast cells and an increase in the plasma cells to 15% (Fig 1). BM trephine showed prominent plasma cells present interstitially as well as in small clumps (Fig 2). Diagnosis of AML with plasmacytosis was considered and further investigations were done to rule out concomitant MM.

Skeletal survey did not show any lytic lesions. Urine examination for Bence-Jones proteins was negative. Serum protein electrophoresis revealed hypoalbuminaemia and a polyclonal increase in gamma globulins. No paraprotein band was detected. Serum free light chain assay was not done due to non availability. Analytical immunocytometry revealed 'AML with differentiation' (FAB type: AML-M2). Cytogenetics showed a normal karyotype. A presumptive diagnosis of AML-M2 with reactive plasmacytosis was made and patient was shifted to the oncology ward but he died the next day before chemotherapy could be initiated. (Total duration of stay at the hospital was 12 days).

Discussion

Reactive BM plasmacytosis is characterized by an increase in the percentage of plasma cells above the normal, i.e. more than 3% but generally it does not exceed 20%.⁵ It is seen in chronic infections, autoimmune diseases, connective tissue disorders, diabetes mellitus and malignancies. Rare causes include angioimmunoblastic lymphadenopathy and multicentric Castleman's disease. In AML, reactive BM plasmacytosis may be due to the presence of either some concomitant, or preceding inflammatory or infectious disorder and the plasma cells are considered to proliferate due to persistent antigenic stimulation.³ Paracrine stimulation by interleukin (IL)-6 secreted by leukaemias cells has also been proposed as a cause.^{2,6,7} Our patient was a known diabetic and patients with diabetes mellitus

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are prone to acute and chronic infections, which might have been responsible for reactive plasmacytosis. AML with reactive plasmacytosis has to be differentiated from a very rare, simultaneously occurring AML with concomitant MM.^{4,7} This is important because the latter requires different therapeutic approach.

Clues from history, clinical examination, and

Table: Causes of AML with plasmacytosis

1. AML with reactive plasmacytosis
a. Due to persistent antigenic stimulation because of infection
b. Due to paracrine stimulation of plasma cells by IL-6 from blast cells
c. Post induction chemo therapy
2. AML with concomitant MM
a. AML secondary to chemotherapy in patient of MM
b. AML with MM without any history of chemotherapy

AML= Acute myeloid leukaemia, IL= Interleukin,
MM=Multiple myeloma

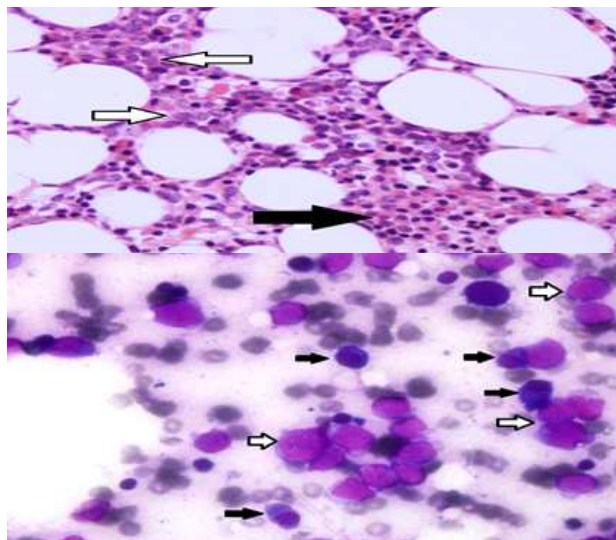


Fig 1: Bone marrow aspirate and trephine showing blast cells and plasma cells indicated by white arrows and black arrows respectively (Magnification: 40x).

presence of a monoclonal band on serum protein electrophoresis, serum free light chain assay, and whole body magnetic resonance imaging (MRI) for bone lesions, help in the diagnosis of a concomitant MM. Our patient did not have any bony lytic lesions, Bence Jones proteinuria, or a monoclonal paraprotein band. Serum free light chain assay was required to rule out myeloma with more certainty but not done due to non availability. Hence our diagnosis of AML with reactive plasmacytosis was

presumptive. Cytological features may help to differentiate reactive plasmacytosis from MM but no discriminatory cut-off value of plasma cells percentage in the BM has been defined. Normally, plasma cells are scattered interstitially and may be seen associated with macrophages and around the capillaries.⁵ In reactive plasmacytosis, the plasma cells have mature nuclear and cytoplasmic characteristics, although binucleate forms may also be seen. A few small clumps may also be seen in case of reactive plasmacytosis but the number of plasma cells in the clumps is generally less than ten.⁵ The presence of plasma cell dysplasia and plasmablasts is strongly suggestive of multiple myeloma. Cytological features in our patient favoured reactive plasmacytosis.

Patients with multiple myeloma (MM) or monoclonal gammopathy of undetermined significance have an increased inherent risk of developing acute myeloid leukemia (AML) which is independent of prior chemotherapy.⁴ A common aetiological agent could be responsible for some cases of concomitant AML and MM. AML is a morphologically, genetically, phenotypically and biologically heterogeneous disorder and plasmacytosis is seen in 6-7 % of cases of AML.² Does AML with reactive plasmacytosis also qualify as a separate entity in the classification of AML? Microscopic examination of the stained smear of BM from a patient of AML with reactive plasmacytosis has distinctively identifiable features comprising of blasts cells and conspicuously increased plasma cells. However no unique clinical, phenotypic, cytogenetic, molecular and biologic properties have been identified to merit its classification as a homogenous separate entity.

Conclusion

AML with plasmacytosis is a heterogeneous phenomenon. Reactive plasmacytosis in AML must be differentiated from AML with MM as the latter requires different therapeutic approach.

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