pISSN: 2220-7562
eISSN: 2617-9482
Recognized by PMDC

JBUMDC

Journal of Bahria University Medical & Dental College

Volume 10 Issue 1, January - March 2020

Bahria University Medical & Dental College Adjacent PNS SHIFA, DHA Phase II, Karachi

JBUMDC
Journal of Bahria University Medical & Dental College
Peer Reviewed Multidisciplinary Quarterly Published Journal
ISSN (print): 2220-7562, ISSN (online): 2617-9482
Recognized by PM&DC (IP/0072)
Online edition is available at URL: https://jbumdc.bahria.edu.pk,
Indexed with Index Medicus for the Eastern Mediterranean Region (IMEMR),
ROAD Directory of Open Access Scholarly Resources at https://portal.issn.org/
Pakmedinet at www.pakmedinet.com/jbumdc,
Google Scholar at https://scholar.google.com.pk/,
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Published by: Bahria University Medical & Dental College

JBUMDC

Journal of Bahria University Medical & Dental College

Journal of Bahria University Medical & Dental College
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DOI: https://doi.org/10.51985/JBUMDC2019129

Dengue: A Recent Challenge In Pakistan

Sannia Perwaiz Iqbal, Sajid Abbas Jaffri

Dengue is one of the fast emerging diseases of humans and is among the most widespread vector-borne tropical viral disease in the world today. The current incidence of dengue infections around the world is more than 58.4 million cases per year with mortality between 10,000 to 20,000. Countries in South Asia and South East Asia have the highest burden of this disease[1]. It is present in more than 128 countries around the world and nearly 4 billion people at the risk of developing this disease[2].

The World Health Organization (WHO) has placed dengue among the 10 most global health problems. Climate change leading to increased flooding and rains, unusually hot and humid whether conditions in certain areas, inadequate control of mosquitos, increased urbanization and rapid growth in population, especially in developing countries are some of the major factors that have been contributing to spread of this disease[3].

In Pakistan, 2019 has been the worst year in the country's history in which more than 44,000 cases have been reported by early November 2019[4]. However, many healthcare professionals believe that these numbers could be much higher as majority of cases in rural areas and slums are never reported.

Dengue fever/Dengue Hemorrhagic Fever is caused by an arbovirus belonging to the flaviviradae family. It is transmitted by the female mosquito Aedes, primarily aegypti and albopictus (daytime feeder) when it bites the human for her blood meal. The virus is a single stranded RNA and has 5 different types. All of these can cause severe illness which can be sometimes life threatening. Each serotype provides a specific lifetime immunity and a short-term cross- immunity against other serotypes. When the mosquito bites the human, the virus gets transferred into the blood stream, where it replicates, especially in target organs and lymphatic tissues. It is then again released and circulates in the patient's bloodstream. When a second mosquito bites the patient it ingests the virus. The virus replicates in the mosquito's midgut and infects its salivary glands. The mosquito carrying the virus then spreads the disease by biting other people. Incubation period is usually around 4 to 7 days (range, 3 to 14 days). Clinical picture can vary from asymptomatic infection to severe life threatening illness. Most important risk factors for the development of severe disease include young age, female gender, prior infection, and certain genotypes of the virus[5].

According to WHO, dengue is classified into 4 clinical syndromes, which include undifferentiated fever, classic dengue fever and Dengue Hemorrhagic Fever/Dengue Shock Syndrome.

The signs and symptoms of classic dengue disease include high grade fever, headache, pain behind eyes balls, severe pain in muscle and joints, nausea and vomiting, rashes on some body parts and dehydration.

Severe dengue occurs in less than 5% of the infected patients. It starts with non-specific symptoms but 4 to 7 days after the onset, plasma leakage with hemorrhagic features could develop causing hypoproteinemia, ascites, peripheral derma, pleural and cardiac effusions. There may be an increase in hematocrit by 20% and thrombocytopenia is also a characteristic feature. There can be bleeding from gums, nose, skin and gastrointestinal track. All of these can progress to severe circulatory collapse, manifested by feeble pulse, low blood pressure, and a pulse pressure of <20 mm Hg. All these changes, may lead to respiratory distress, compromised mental status, coma and death. DHF/DSS has a 5% mortality rate and children and elderly are at the greatest risk[5,6].

It is noteworthy that platelet deficiency is rarely the cause of death in people afflicted by this disease.The primary cause of death in patients suffering from dengue is the capillary leakage, leading to blood deficiency in the intravascular compartment, followed by multi-organ failure. Persistent vomiting decreased level of consciousness, severe abdominal pain and sudden decrease of body temperature to hypothermia are warning signs of serious condition of the patient.

Dengue is a self- limiting disease and recovery can take place between 2 to 7 days, however, there is no specific drug therapy. The main goal of treatment is to prevent shock, provide basic supportive measures which include giving fluids either by mouth or intravenously throughout the illness. Patients suffering from dengue should seek medical advice, rest and drink plenty of fluids in the form of juices and drinks. Paracetamol can be taken to bring down fever and reduce joint pains. NSAIDs should be avoided as they can affect the platelet function thereby leading to the risk of bleeding[7]. Platelet transfusion is usually not required unless the counts drop below 10,000 and there is some evidence of spontaneous and active bleeding. At first instance of

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Received: 04-12-2019
Accepted: 23-12-2019

plasma leakage from the intravascular compartment to the extravascular compartment, fluid replacement amounting to 20 ml per kg body weight per hour must be carried out and continued till the difference between the systolic and diastolic blood pressure is over 40 mmHg, or the patient passes adequate volume of urine. It has been suggested to utilize the formula of 20, when treating patients with dengue. 'Formula of 20' i.e. rise in pulse by more than 20; fall of more than 20 mmHg in upper and lower blood pressures and presence of more than 20 hemorrhagic spots on the arm after a tourniquet test, implies a high-risk situation and the patient would need immediate medical attention. Dengue can be diagnosed by detection of the virus in serum (serology) using ELISA, detection of IgM antibodies in blood by PCR (Polymerase Chain Reaction) etc. The best test for dengue is the DENGUE NS-1. The test is mostly positive from day 1 to day 7 after infection and cannot be false positive[8].

In order to increase the number of platelets, certain herbal treatments have been documented. There is evidence that the aqueous extract of leaves of Carica papaya plant given 3 times a day would significantly increase the number of platelets[9]. However, in a recent systematic review and meta-analysis on the use of papaya leaves extract in dengue has questioned in terms of real efficacy of this treatment, and large scale clinical trials with focus on its role in preventing plasma leakage from intravascular compartment to extravascular compartment, prevention of shock and possible side-effects have been suggested[10].

The only way to prevent dengue transmission is to combat the vector mosquitoes and limiting exposure to mosquito bites. It should be remembered that dengue breeds in clean stagnant water, therefore mosquito breeding places such as empty flower pots, open water tanks etc. should be either eliminated or properly covered. There should be provision of reliable water supply and regular garbage collection. Personal protection from mosquito bites can be achieved by using insecticide sprays in the house and mosquito repellents and covering most of the body parts especially after the monsoon season. Health education campaigns for the masses using the electronic and print media have always been helpful.

A novel vaccine for dengue has been prepared in a number of countries, however it is not commercially available as yet especially in the developing countries of South Asia[11]. Therefore, it is imperative that the health authorities in these countries must carry out emergency vector control programs and robust surveillance during disease outbreaks.

As per WHO, the recent ongoing outbreak of dengue in Pakistan has resulted in 47,120 confirmed cases and 75 related fatalities. In such a scenario, it is extremely important that the healthcare providers identify these cases early, provide necessary treatment and also educate the public at large on its prevention[12].

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019051

Effectiveness Of Urine Dipstick In Diagnosis Of Pre-eclampsia

Ferhat Uzair, Urooj Naz, Samia Shuja, Abdul Waheed, Tahira Assad

ABSTRACT

Objective: To determine the efficacy of urine dipstick in Pre-eclamplasia.

Study Design and Setting: This was a cross-sectional study conducted at the department of obstetrics & gynecology of a tertiary care hospital from May-2017 to September-2018.

Methods: All the pregnant women of age 15-45 years, BP=140/90 mmHg on two occasions 4 hours apart or single diastolic value of 100 mmHg, gestational age >20 weeks, singleton pregnancy, booked in first trimester of pregnancy were included in the study. Statistical package SPSS 22 was used for the analysis of data chi-square tests were applied for the diagnostic accuracy of urine dipstick in detection of Pre-eclampsia in pregnant women. P-value was <0.05 was considered as significant.

Results: Total 211 pregnant women were enrolled in the study. Mean (SD) age was 28.26(3.86) years. Overall sensitivity and specificity of urine dipstick was found to be 94% and 95.4% respectively, positive predictive value 95%, negative predictive value 94.5% and excellent diagnostic accuracy 94.7% of urine dipstick was observed for the diagnosis of spot urine protein creatinine ratio

CONCLUSION: Urine dipstick found to be sensitive and reliable test to screen pre-eclampsia

Key words: Diagnostic accuracy, Pre-eclampsia, Sensitivity, Specificity, Spot urine protein creatinine ratio, Urine dipstick

INTRODUCTION:

Pre-eclampsia is a common hypertensive disorder of pregnancy and it affects around 3-14% of all pregnant women worldwide.[1] In most of the developing countries around 40,000 pregnant women die each year due to pre-eclampsia.[1,2] In developing countries, it is estimated that about 40-60% of maternal death occur due to pre-eclampsia. Pre-eclampsia is the illness that arises only during pregnancy.[3] It occurs most commonly in women having their first pregnancy. A woman who had pre-eclampsia during first pregnancy has 25-50% chances of developing it again in later pregnancies.[4,5] Women at extremes of age such as teenagers and women over 40 have higher risk of developing this condition.[4,5]

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Received: 21-05-2019
Accepted:15-11-2019

However, the statistics from Pakistan are limited. In Pakistan the incidence of pre-eclampsia is 7%. Pre-eclampsia is rated as the 3rd leading source of death related to pregnancy, after hemorrhage and embolism.[6]

Roberts CL et al (2011) showed that the rates of pregnancy hypertension and pre-eclampsia declined over time in most of the population of northern Europe and Australia from 1997 to 2007 (3.6% to 9.1% and 1.4% to 4.0% respectively).[7]

In 2014, a systemic review done by World Health Organization (WHO) on global causes of maternal death reported that hypertensive disorders accounted for 14% of maternal deaths worldwide. In developed regions it accounted for 12.9%, 14% in developing regions, 16.9% in Northern Africa, 16% in Sub-Saharan Africa, 10.4% in Eastern Asia, 10.3% Southern Asia, 14.5% in Southeastern Asia, 13.4% Western Asia, 14.7% in Caucasus and Central Asia, 22.1% in Latin America and Caribbean and 13.8% in Oceania.[8]

Urine dipstick is a rapid, inexpensive and easy to use tool. However the results of dipstick provide low sensitivity and specificity for urine protein excretion over 24 hours[9]. Urine collection over 24 hours is considered the traditional comparator for quantification of proteinuria in pregnancy, when significant proteinuria is defined as 0.3 g/day or more.[10] This is the traditional technique and considered as Gold standard, but it has many disadvantages. It is time-consuming and expensive. [11]

In Pakistan, urine dipstick for all cases of suspected pre-clampsia is practiced due to quickest and cheapest method of assessing proteinuria. But previous studies showed a wide range of sensitivity and specificity. There is a wide variation

in the results of different studies. There is much need to determine its effectiveness in determining proteinuria in diagnosis of pre-eclampsia as the cost of 24 hours urine protein test is much higher as compared to spot urinary protein to creatinine ratio. Present study was specifically designed to evaluate the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of urine dipstick in Pre-eclamplasia.

METHODOLGY:

This was a cross-sectional study conducted at the department of obstetrics & gynecology of a tertiary care hospital from May-2017 to September-2018. According to diagnostics accuracy sample size calculator by taking sensitivity of urine dipstick 80%, specificity 95%, margin of error for sensitivity i.e (d) 16%, for specificity 3%, confidence interval 95%, level of significance 5%, then the estimated sample size was (n= 211) selected women were advised to collect midstream urine. Dipstick test was performed and same sample were sent to laboratory for urine protein creatinine ratio. Finding on Urine dipstick if proteinuria of > 300 mg and significant proteinuria is > 0.3 is considered positive in pre-eclampsia . The procedure was considered to be true positive (TP) when UPr/Cr ratio is > 0.3 mg/dl, urine dipstick is >300 mg. True negative were categorized with cut off when UPr/Cr ratio is <0.3 mg/dl, urine dipstick is <300 mg. Those female patients with history of renal diseases, hepatic diseases, diabetes, endocrine diseases, autoimmune diseases, illicit drug use or by any other medical illness were excluded. Patients with LMP not known and no dating scan available were also not considered. Data feeding and analysis were on SPSS version 22. Mean and standard deviation were calculated. Age, parity, gestational age, frequencies and percentages were calculated for finding of urine dipstick and protein creatinine ratio. A 2x2 tables was constructed to calculate sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of urine dipstick. Chi-square test was applied. P value < 0.05 was considered as significant.

RESULTS:

Total 211 pregnant women were enrolled in the study. Mean (SD) age was 28.26(3.86) years and mean (SD) gestational age was 27.18(3.61) weeks. Average height and weight was 60.01 inches and 75.84 kg respectively. Mean (SD) gravida and parity was 2.14(1.01) and 3.04(1.77) respectively. Mean (SD) SBP and DBP was 156.85(7.06) and 96.53(3.50) mmHg respectively. When the age was distributed by three interval from 15 years to 25years, it was observed that smallest age group was between 36-45 years (12%) and included twenty five 25 women. The group having largest number of women was between 26-35 years (58%) and included 122 women. Almost 121(57%) women had gestational age between 26-35 weeks. Out of 211 patients, 100(47.4%) women were recorded positive on the basis of urinary dipstick ratio>300 mg and 101(47.8%) on spot urine creatinine ratio having cut-off >0.3 mg/dl respectively.

Overall sensitivity and specificity of urine dipstick was found to be 94% and 95.4% respectively, positive predictive value 95%, negative predictive value 94.5% and overall diagnostic accuracy was 94.7%.

DISCUSSION:

Pre-eclampsia the most common hypertensive disorder victimizing 3-14% women worldwide.[12,13] There are several methods for diagnosing pre-eclampsia[14,15]. One of the widely used methods is urine dipstick. The advantage of the dipstick

Table 1: Descriptive and demographic characteristics

VARIABLE	Mean	Standard Deviation	Min-Max
Age (Years)	28.26	±3.86	24-41
Gestational Age (Weeks)	27.18	±3.61	22-36
Height (Inches)	60.01	±3.74	54-66
Weight (Kg)	75.84	±19.08	38-110
Gravida	2.14	±1.01	0-4
Parity	3.04	±1.77	1-7
SBP (mmHg)	156.85	±7.16	145-169
DBP (mmHg)	96.53	±3.50	92-103
Urine Dipstick ratio			
<300(mg)	111(52.6%)		
>300(mg)	100(47.4%)		
Spot urine creatinine ratio			
<0.3(mg/dl)	110(52.2%)		
>0.3(mg/dl)	101(47.8%)		
Maternal Age			
15-25 years	64(30%)		
26-35 years	122(58%)		
36-45 years	25(12%)		
Gestational Age			
<25 Weeks	71(34%)		
26-35 Weeks	121(57%)		
>35 Weeks	19(9%)		

Table 2**:** Effectiveness of urine dipstick in detection of preeclampsia

Dipstick Ratio	Spot urine protein creatinine ratio		Total
	>0.3 mg/dl	<0.3 mg/dl	
>300	95(TP)	5(FP)	100(47.40%)
<300	6(FN)	105(TN)	111(52.6%)
Total	101(47.8%)	110(52.2%)	211(100%)

Sensitivity = (95÷ 101) × 100 = 94.0%,
Specificity = (105 ÷ 110) × 100 = 95.4%
Positive predictive value = (95 ÷ 100) × 100 = 95%,
Negative predictive value = (105÷111) × 100 = 94.5%
Diagnostic Accuracy = (95+105) ÷211=94.7,
P-value<0.001*

Table 3 Diagnostic accuracy of Urine Dipstick with age and gestational age

Age groups	Sensitivity	Specificity	PPV	NPV	Accuracy
Age< or =30 Years	82.80%	83.30%	85.20%	80.60%	83%
Age>30 Years	80.60%	86%	78.1%	87.7%	83.90%
Gestational Age					
Gestation period<or =28 Weeks	84%	93.30%	93.30%	85.70%	88.40%
Gestation period >28 Weeks	49.00%	66.10%	45.40%	70.40%	58.60%

test is that it can be done anywhere by any trained paramedical or medical personnel while the urinary protein/creatinine ratio, require laboratories and trained laboratory personnel. But the diagnostic accuracy of urine dipstick for the diagnosis of pre-eclampsia is debatable.[16,17]

There are several studies who recommended urine dipstick but many studies found other methods more reliable than urine dipstick. Eigbefoh (2006)[9], Archanakumari et-al (2013)[16], Park(2013)[18],Kumari(2013)[16] and Jan, S., et al. (2017)[19] have showed that urine dipstick is unreliable and poorly correlates with quantitative urine protein determinations. They recommended using protein creatinine ratio. On the other hand Zibaeenezhad, M. J., et al [20,] Uzan, J.[21] and Morris, R., et al. (2012)[22] showed good diagnostic accuracy of urine dipstick.

Zibaeenezhad, M. J., et al. (2010)[20] showed that the sensitivity, specificity, positive and negative predictive value of urine dipstick was 80%, 95%, 22.2% and 99.6% respectively. Whereas, Nischintha, S., et al. (2014) reported sensitivity 74% and specificity 89% another study by Chotayapom (2011)[23,24] reported sensitivity 56% to 80% and specificity 67% to 92% respectively.

In this study, urine dipstick is found to be a reliable method with overall sensitivity of 94%, specificity of 95.4%, positive predictive value 95%, negative predictive value 94.5% and diagnostic accuracy of 94.7%. Urine dipstick was found to be reliable and have good diagnostic accuracy in age groups =30 and >30. According to gestational age, urine dipstick had very low diagnostic accuracy for gestational age >28 weeks whereas, good diagnostic accuracy was observed for gestational age =28 weeks.

Our study has added an evidence to the literature that urine dipstick is reliable in detecting pre-eclampsia in pregnant women with high sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy.

Conclusion: Urine dipstick found to be sensitive and reliable test to screen pre-eclampsia.

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019110

Comparison Of Patient Satisfaction Between New Complete Denture Wearers And The Old Ones

Zarah Afreen, Shoaib Rahim, Ammarah Afreen, Umer Javed, Aamna Khalil, Sadia Daaniyal

ABSTRACT

Objective: To determine the mean satisfaction score for patients with complete dentures and to compare the mean satisfaction score of patients with complete dentures and without past denture experience.

Study design and Setting; It was a cross-sectional study conducted at Watim Dental College, Rawalpindi, from March to August 2018.

Methodology: A total of 98 patients were selected and were asked regarding previous history of denture usage and their experience with the new set of dentures; in terms of function, comfort, appearance and total satisfaction. As a protocol all patients presenting to outpatient department and those patients who fulfilled the criteria were referred to Prosthodontic department for provision of complete dentures by specialist prosthodontist. Data was analysed using SPSS version 20. Descriptive statistics were calculated for both qualitative and quantitative variables. For qualitative variables like gender frequency and percentages was calculated. For Quantitative variables like age, score of function, comfort, appearance and total satisfaction mean and standard deviation were calculated. Mean± SD was calculated for satisfaction score among patients with and without past experience of denture usage. Independent sample t-test was used to compare quantitative variables. P values of less than 0.05 was considered significant.

Results: Mean score of function, comfort, appearance and total satisfaction was greater among the patients with past denture experience as compared to new denture wearers with no past experience of denture wearing.

Conclusion: Past denture experience has significant effect on patient satisfaction with their new complete dentures.

Keywords; Complete denture wearers, patient satisfaction, past denture experience.

INTRODUCTION:

There is a significant co relation between oral and general health, which subsequently affects the overall quality of life of people especially the elderly people. The oral health of a population can be well indicated by partial or complete edentulism.[1] One of the major concerns among elderly population worldwide is edentulism, although over the last few years the incidence of complete tooth loss has markedly decreased.[2] However, the different regions of the world have shown considerable variations in the prevalence of complete edentulism.[3] Direct consequences of edentulism include impaired masticatory function, discomfort, nutritional deficiencies, poor oral health quality, psychological and social disability.[4]

Conventional complete denture therapies still extensively used and it is not expected to decline in the near future especially in less developed population with limited economic resources.[5] Rehabilitation with dentures following tooth loss may result in great amount of impact and social implications on the patient.[6] The ability of the patient to interact with others can also be restored with the help of dentures.[7] The prosthetic rehabilitation is mainly provided to those who have experienced tooth loss in order to restore function, comfort, aesthetics and oral health. Clinicians believe that supporting tissues can be maintained in good health by means of well-fitting dentures and in this way oral function and self-esteem of the patients can be improved. [8]

Patient satisfaction is considered as one of the most important goals in prosthodontic treatment. The factors which mainly affects the stomatognathic system are the quality of dentures, oral conditions, patient's acceptance towards the dentures, patient's personality and the patient-dentist relationship.[9] The influence of patient expectations on the patient satisfaction must be determined as it has a crucial effect on the success of the treatment.[8] Different results were shown in different studies when these factors were examined. Some investigators did not find a significant relationship while

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Received: 08-10-2019
Accepted: 12-12-2019

others did .[10,11] The success of complete dentures is dependent on multiple factors, patient perception is an important factor for successful treatment.[12] Satisfaction towards complete dentures may not only be affected by biologic and technical considerations taken into account during fabrication of complete dentures, other parameters may also play an important role. These include age, gender, literacy level, socioeconomic conditions, marital status, patient/professional relationship and psychological factors.[13,14]

Patient satisfaction is also affected by a large number of factors. Previous experience with dentures and age of patient are considered important factors. One study concluded that patients greater than sixty years of age showed greater difficulty in adaptation to the new set of complete dentures than those who were younger than sixty.[15] The oral mucosal disorders which are frequently associated with aging and denture usage includes denture stomatitis, angular cheilitis, oral fungal infections, and traumatic ulcers.[16-18]

The rationale of this study was to evaluate the effects of denture on patient satisfaction with new set of dentures. One of the important determinants for success of complete denture therapy is past denture experience, therefore it should be considered during evaluation and assessment of completely edentulous patient. This study was aimed to determine the mean satisfaction score for patients with complete dentures and to compare the mean satisfaction score of patients with complete dentures with and without past denture experience.

METHODOLOGY:

It was a cross-sectional study conducted at Watim Dental College, Rawalpindi, from March to August 2018.

The ethical approval from the hospital ethical committee was obtained prior to the study. The subjects were selected via non-probability consecutive sampling. Inclusion criteria consisted of both male and female patients with age ranging from 35-80 years, who were selected for provision of complete dentures with or without any previous history of denture use. Exclusion criteria consisted of patients with a history of maxillofacial trauma, Parkinson's disease, myasthenia gravis, bulbar palsy, hyposalivation or xerostomia, terminally ill patient, non-cooperative or mentally debilitated patient and patient using antipsychotics or antidepressants, muscle relaxants. As a protocol all patients presenting to the hospital were examined in OPD and those patients who fulfilled the criteria were referred to Prosthodontic department for provision of complete dentures by specialist prosthodontist.

A total of 98 patients were selected for this study based on above mentioned criteria and were asked regarding previous history of denture usage. The dentures were fabricated by a single prosthodontic laboratory technician in the hospital. All subjects were instructed to wear their dentures during waking hours and to remove them before sleeping at night. Oral hygiene instructions were provided. Patients were requested to return after one week after insertion and were interviewed by principal investigator for answering questions which were given in the questionnaire regarding their experience with the new set of dentures, in terms of three categories, that is, function which consisted of drinking, chewing, biting and speaking; comfort which consisted of denture tightness (in both arches), gagging and denture comfort in both arches; and appearance which consisted of shape of teeth, shade of teeth and general appearance. A five- point scoring system (poor=1, fair=2, good=3, very good=4 and excellent=5) was used. Total satisfaction score, out of 60, was calculated based on the scores in these three categories and filled in the proforma (function score= 20, comfort score= 25 and appearance score= 15). Follow up was ensured through telephonic contact.

Data was analysed using SPSS version 20. Descriptive statistics were calculated for both qualitative and quantitative variables. For qualitative variables frequency and percentages was calculated. For Quantitative variables mean and standard deviation were calculated. Mean± SD was calculated for satisfaction score among patients with and without past experience of denture usage. Independent sample t-test was used to compare quantitative variables. P values of less than 0.05 was considered significant.

RESULTS:

A total number of 98 patients were selected for this study out which n=52 (53.1%) were male and n=46 (46.9%) were female. . The frequency distribution of patients is given in Figure-I. Among these n=98 patients 52.04% (n=51) were new denture wearers with no previous denture experience and 47.96% (n=47) were old denture wearers with previous experience of denture use. Mean+SD Scores for Function, Comfort and Appearance and total satisfaction score were calculated as shown in Table-I.

Independent sample t-test was applied to determine the difference in the scores for function, comfort and appearance for patient who had previous experience with denture wearing and those who had no experience and p-value was calculated as given in Table-II. As can be depicted from the table, the average scores for the patients who were new denture wearers were lower than those who had past denture experience for all tested variables. Independent sample t-test was applied to determine the difference in total satisfaction score between both genders and p-value was 0.024. Independent sample t-test was used to determine the difference in satisfaction score between age (which was grouped into 35-57 years and 58-80 years for this test) and a p-value of 0.001 was found to be significant.

DISCUSSION:

Patient satisfaction with their dentures is a complex phenomenon which is influenced by various factors. In addition to psychological factors, various other factors have an influence on patient satisfaction.[19] The concept of success

of dentures were judged by the dentists and patients in a different way. Technical standards are considered the key point for the success of denture by the dentist. In contrast to this, patients evaluate them from the viewpoint of personal satisfaction. The patients who were well satisfied in their lives are also more satisfied with their dentures.[20] A patient self-assessment questionnaire allows patients an opportunity for discussing and sharing their viewpoint with their clinician,

Figure-I: Histogram Showing Frequency Distribution of Patients

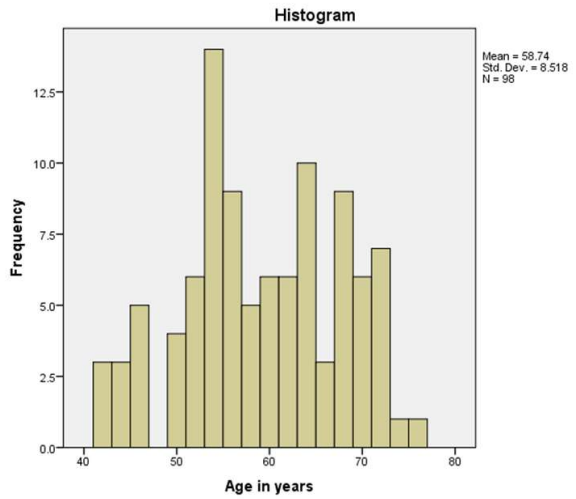

Table-I: Mean and Standard Deviation of Scores For Total Satisfaction Comprising Of Function, Comfort And Appearance

Category	Score	
	Mean	Standard Deviation
Function		
Drinking	3.01	0.902
Chewing	2.87	0.893
Biting	2.87	0.949
Speaking	3.36	1.048
Functional Satisfaction	12.153	2.822
Comfort		
Upper denture tightness	3.46	1.047
Lower denture tightness	2.76	0.850
Gagging	3.46	0.910
Upper denture comfort at rest	3.37	0.817
Lower denture comfort at rest	2.86	0.849
Comfort Satisfaction	15.877	3.026
Appearance		
Shape of teeth	3.31	0.913
Shade of teeth	3.31	0.913
General Appearance	3.57	0.952
Appearance Satisfaction	10.153	2.299
Total Satisfaction	38.193	7.311

Table-II: Independent Sample T-Test of Scores For Total Satisfaction Comprising Of Function, Comfort And Appearance Between New Denture Wearers And Old Denture Wearers

Denture Experience	Score				P-value
	Old Denture Wearer N=47		New Denture Wearer N=51		
Category	Mean	Standard Deviation	Mean	Standard Deviation	
Function					
Drinking	3.53	0.80	2.53	0.70	0.001
Chewing	3.26	0.84	2.51	0.78	0.001
Biting	3.36	0.76	2.41	0.87	0.001
Speaking	3.89	0.78	2.86	1.02	0.001
Functional Satisfaction	14.021	1.95	10.431	2.37	0.001
Comfort					
Upper denture tightness	3.96	0.85	3.00	1.00	0.001
Lower denture tightness	3.19	0.77	2.35	0.72	0.001
Gagging	3.85	0.75	3.10	0.90	0.001
Upper denture comfort at rest	3.72	0.65	3.04	0.82	0.001
Lower denture comfort at rest	3.15	0.75	2.59	0.85	0.001
Comfort Satisfaction	17.851	1.76	14.058	1.95	0.001
Appearance					
Shape of teeth	3.83	0.56	2.82	0.91	0.001
Shade of teeth	3.77	0.69	2.88	0.88	0.001
General Appearance	4.06	0.67	3.12	0.95	0.001
Appearance Satisfaction	11.617	1.26	8.803	2.21	0.001
Total Satisfaction	43.510	3.68	33.294	6.33	0.001

hence it is used in this study.[21]

According to a study by Samara RM, little influence is exerted on patient's acceptance of the new set of dentures by gender variation, although females appear to be a little more critical with their dentures as compared to males, particularly in terms of aesthetics.[9] In our study a significant difference was noted in the total satisfaction score among males and females, which was not in agreement with a study by Knezovic-Zlataric and colleagues. This difference may be because of the difference in the population ethnicity as their study was conducted on Croatian adults, which further enforces the effect of geographic variability on population satisfaction. Although further studies on larger population may need to be conducted for confirmation.[21] Current study results are consistent with another study carried out by Rania M Samara, at Princess Ayesha Medical Complex / Royal Medical Services, over a period of two years.[9] Significantly higher mean scores were recorded in patients who have previous denture experience. The results of this study showed that patients with additional set of dentures exhibited improved function and comfort. In addition to this, patients appear to be more satisfied with their new denture aesthetics as well as they have more realistic expectations regarding aesthetics. Furthermore, the speaking ability also tends to be improved in these patients.[9]

The mean score of total satisfaction in this study was 43.5±3.68 for old denture wearer which was much higher than new denture wearers (33.29±6.33) and it was statistically significant and consistent with scores of another study and was also found to be significant.[10] According to this study the mean score of function was found to be higher (14.02 ± 1.95) among old denture wearer as compared to new denture wearers (10.43±2.37). It is found to statistically significant. This result is also comparable to another study in which mean score of function among old denture wearer was higher (19.30±1.436) as compared to new denture wearer (17.23±2.54).[9]

The mean score of comfort was found to be higher (17.85 ± 1.76) among old denture wearer as compared to new denture wearer (14.05± 2.05). This result is also comparable to another study in which mean score of comfort among old denture wearer was higher (24.40±0.836) as compared to new denture wearer (22.56±2.39).[9] The mean score of appearance was 11.61±1.26 for old denture wearer which is much higher than new denture wearers (8.80± 2.21). Mean score of appearance among the old denture wearer was found to be 14.84± .561 as compared to new denture wearer 14.59± .959.[10] This result was not consistent with the result of our study because although the value was found to be higher among the old denture wearer as compared to new denture wearer, the result was not found to be significant.

Another study was conducted at Liaquat University Hospital Hyderabad and Jamshoro to evaluate the factors which influence the patient's satisfaction with removable dentures. Sixty-six patients of both genders were included. More than 55% of the patients were comfortable with their dentures. 65 to 80 % patients showed their satisfaction in terms of retention, stability, speech, taste, chewing and communication. While 86.7% subjects experienced no pain or discomfort and 60% of subjects did not have a foreign body feeling with the use of dentures. Furthermore, 53.3% felt they will recommend the treatment to others. According to this study, the satisfaction scores were considerably higher in patients who were provided with the set of dentures for the first time.[19]

The limitations of this study included patient over a larger age group were selected, that is, 35-80 years, the status of residual alveolar ridge was not considered and the quality of previous complete dentures were not evaluated or considered in subjects who were old denture wearers. Improved stability and function of prosthesis can be seen in those patients who have an additional set of dentures. It might be due to a more developed neuromuscular control over their dentures. Speaking ability appears to be improved and these patients tend to have more realistic expectations in terms of aesthetics.

CONCLUSION:

Past denture experience has significant effect on patient satisfaction with their new complete dentures.

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019068

Relationship of Timings and Outcome of Tracheostomy Among Patients Requiring Prolonged Mechanical Ventilation

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ABSTRACT

Objective: To assess the indications of tracheostomy among patients requiring prolonged mechanical ventilation and to observe the relationship of the timings and outcome of tracheostomy with age and gender.

Study Design and Setting: It was a descriptive study conducted at intensive care unit (ICU) of Department of Otorhinolaryngology at Bahawal Victoria Hospital from January 2017 to December 2018.

Methodology: Secondary data was collected with the help of charts of ICU patients in which elective tracheostomy was done to replace orotracheal intubation for mechanical ventilation. Inclusion and exclusion criteria were designed. Clinical record was reviewed for the assessment of indications of the procedure (medical or surgical) along with age and gender distribution. The timing of tracheostomy in these patients with its outcome in terms of decannulation and weaning were recorded. Proforma was used to enter the findings. Finally results were obtained and assessed on SPSS Version 23.

Results: Out of total 551 tracheostomies 42(7.6%) were indicated for the patients of ICU requiring prolonged mechanical ventilation. From the 42 mechanical ventilated patients majority had Guillain-Barre syndrome (GBS) 20(47.6%). Twenty six patients were adults (61.9%) and sixteen were children (38%).Twenty four were male patients (57.1%) and eighteen were females (42.8%). The timing of tracheostomy among majority of the patients (40) was from 7-10 days, with mean of 9th day with good outcome. Only two patients who underwent tracheostomy after two weeks had to face poor outcome (failed decannulation, late weaning) (4.7%).

Conclusion: Neuroparalytic lesions were the common indication among the patients requiring prolonged mechanical ventilation with tracheostomy. Tracheostomy if performed earlier in such patients carries good outcome.

Key Words: Decannulation, Intensive care unit, Mechanical ventilation, Tracheostomy, Weaning

INTRODUCTION:

Tracheostomy is one of the most commonly performed surgical procedures in the critically ill patients[1]. It is also one of the oldest operations as Asciepiades of Persia used to perform tracheostomies some 4000 years ago[1,2]. The initial most reference of this procedure can be located in the Rig-Veda written in 1500 BC[2]. The procedure was considered dangerous and carried hazards till the initial part of 19th century therefore rarely performed[3]. It was Chevalier Jackson who first mentioned the modern classic surgical technique for tracheostomy in 1909[2]. Tracheostomy has been believed to be a safe, effective and single life saving procedure during the past three decades[3]. The indications of tracheostomy can be emergency or elective[3]. Being an elective procedure tracheostomy is commonly performed in the patients of intensive care unit (ICU), requiring prolonged mechanical ventilation[4]. Almost 10% of the patients in ICU having mechanical ventilation require tracheostomy[5,4]. The advantages of tracheostomy over orotracheal intubation in the patients with mechanical ventilation may be the reduction of anatomical dead space, low incidence of oral and laryngeal ulceration, more patient comfort and ability to communicate[6,7]. There are many surgical and medical causes for which patients require prolonged assisted ventilation with tracheostomy. Poliomyelitis, respiratory muscle paralysis, Guillain Barre syndrome (GBS), coma, neuromuscular diseases, sepsis and chronic obstructive pulmonary disease (COPD) can be the common medical causes[3,4]. Surgical causes may be some postoperative surgical complication or any non surgical trauma[4,6]. Head injury or Traumatic brain injury (TBI) is the usual cause in non-surgical category where patients require prolonged mechanical ventilation with tracheostomy[5].

The timing of tracheostomy in all these patients with prolonged mechanical ventilation has been a matter of controversy thus remains unclear[8]. However early tracheostomy results successful decannulation and weaning from ventilator and vice verca[9]. Moreover the selection of patients is also important as those with head trauma or traumatic brain injury, tracheostomy as early as possible

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Received: 01-06-2019
Accepted: 19-11-2019

after the start of mechanical ventilation is advocated[5,9]. Worldwide; various different studies have been carried out on this subject but focusing mainly on the timing of elective tracheostomy and their short term outcomes in the mechanically ventilated patients[8,2,6]. Some of studies are done exclusively in mechanically ventilated children and infants[9,10]. In Pakistan the first study has been reported and carried out by Prem Kumar et al assessing the outcomes and complications of elective tracheostomy in children who were mechanically ventilated[11]. Therefore; the rationale of our study was to assess the indications for tracheostomy, effects of its timing among all age group and gender requiring prolonged mechanical ventilation in our settings and to assess the medical or surgical indications among the patients requiring prolonged mechanical ventilation with tracheostomy, effects of its timing among all age group and gender in our settings.

METHODOLOGY:

It was a descriptive study conducted at intensive care unit (ICU) of Department of Otorhinolaryngology at Bahawal Victoria Hospital from January 2017 to December 2018.Secondary data was collected with the help of charts of ICU patients in which elective tracheostomy was done to replace orotracheal intubation for mechanical ventilation. After the formal permission from the hospital ethical committee; the records were reviewed for all the patients irrespective of age and sex group from the main intensive care unit of Bahawal Victoria Hospital. Patients below 15 years of age were taken as children.

Operational Definitions: Tracheostomy: Surgical procedure in which anterior tracheal wall is opened at the level of second third and fourth ring and connecting the opening with the skin by Tracheostomy tube.

Prolonged mechanical ventilation: It is the assisted positive airway pressure ventilation given to the patient with the help of ventilator for more than a week.

Decannulation: It is the reversal of tracheostomy intubation when the patient is free of initial causative disease / factor and becomes able to maintain normal spontaneous respiration through the upper airway. When this is achieved it is rendered as successful decannulation and if patient cannot maintain normal respiration through upper airway after removing the tracheostomy tube out even if causative disease / factor persists no more is considered as failed decannulation.

Weaning: It is shifting of the patient from assisted mechanical ventilation to normal spontaneous respiration. It is measured in terms of early or late weaning.

Timing of Tracheostomy: It is the time / day when the orotracheal intubation is replaced by the tracheostomy tube insertion after doing tracheostomy. It is counted from the day one when the patient is placed on mechanical ventilation through orotracheal intubation.

All the patients during the mentioned duration irrespective of any age and sex were included in the study. There Physicians were requsted to do tracheostomy in ICU to prolong mechanical ventilation. Tracheostomy was performed by orotracheal tube which was replaced by tracheostomy tube through which the mechanical ventilation continued. All those patients who got emergency tracheostomy first and later on after few hours or days shifted to mechanical ventilation because of the failure of maintaining effective oxygen saturation through spontaneous respiration were excluded from the study as our study focused on the timing of the elective tracheostomy and all those patients who expired despite having elective tracheostomy and assisted mechanical ventilation in ICU were also excluded from the study. This was because the assessment of parent disease mortality was not the purpose of this study. As to assess the outcome of tracheostomy in terms of decannulation and weaning in mechanically ventilated patients was one of the prime objectives and not the mortality because the mortality is generally not due to the tracheostomy and its timing but due to the severity of initial causative disease.

The medical records of all those patients meeting the above mentioned inclusion and exclusion criteria were collected from the intensive care unit of the hospital for required information. Age, Sex, initial medical or surgical disease, timing of elective tracheostomy after orotracheal intubation, place of elective tracheostomy, time of weaning from mechanical ventilation and patterns were noted on a separate Proforma.

Frequencies were used to express the descriptive variables, SPSS version 20 was used to analyze data.

RESULTS:

During the previous two years of study total 551 patients underwent tracheostomy. Out of these, 42(7.6%) patients got elective tracheostomy on the request of attending physician of ICU for the purpose of prolonged mechanical ventilation. From these 42 patients were initially on endotrachealintubation for mechanical ventilation which was later on replaced by tracheostomy tube after tracheostomy. Elective tracheostomy of all these patients was performed in operation theatre. Regarding the indications of this procedure; it was found that 20 out of 42 (47.6%) patients were having Guillain Barre Syndrome(GBS) , 07(16.6%) patients were of encephalitis and in 06 (14.2%) patients was indicated due to tetanus. Cerebrovascular accident (CVA) was found in 02(4.7%) patients, Traumatic brain injury (TBI) was present in 02(4.7%) patients and 02(4.7%) patients were found with Para Phenylene Diamine (PPD / Black stone) poisoning. Myasthenia gravis, acid ingestion and HELLP syndrome were present in one patient equally (2.3%). (Table 1). Regarding age distribution 26(61.9%) patients were adults and 16(38%) were children (38 %). Mean age was 22 years. GBS was the most common indication among the two age group of adult 11(42.3%) and

children 9(56.2%) respectively-(Table 1). In this study; 24 (57.1%) were male patients and 18(42.8%) females. Again GBS was the most common indication among both genders-(Table 2).

The time when the elective tracheostomy was performed on these 42 patients was also recorded and mainly this was dependent on the request of attending physician of ICU. The time when elective tracheostomy was performed ranged between 7-10 days among 40 patients except 02 patients (4.7%) where the request for the procedure was sent beyond 02 weeks, one on 20th day and second on 25th day of mechanical ventilation with orotracheal intubation and the mean was 9th day. All those patients (40) who were operated and shifted to tracheostomy tube from orotracheal tube between 7-10 days were weaned off from mechanical ventilation earlier (within one month) after ICU management (95.2%) and likewise were successfully decannulated at the time of discharge. 02 patients (4.7%) who were operated for elective tracheostomy on 20th& 25th day both had to face difficulty in early weaning and failed decannulation of tracheostomy tube(100%) and hence their hospital stay was prolonged. Out of these 02 patients one patient was of head trauma (TBI) and one was of CVA (50%) (Graph 1). There was no drop out in the results.

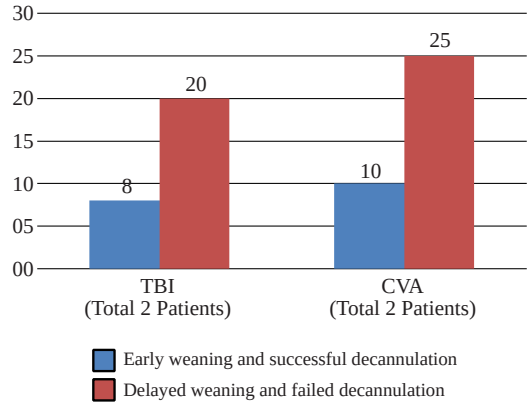
Table 1: Elective Tracheostomy in Adults and Children with Indications

Indications	Adults (26 Patients) (69.9%)	Children (16 Patients) (38%)	N=42
GBS	11 (42.3%)	9 (56.2%)	20 (47.6%)
M.Encephalitis	05(19.2%)	02(12.5%)	07(16.6%)
Tetanus	03(11.5%)	03(18.7%)	06(14.2%)
CVA	02(7.6%)	-	02(4.7%)
PPD	02(7.6%)	-	02(4.7%)
TBI	01(3.8%)	01(6.25%)	02(4.7%)
M.Gravis	01(3.8%)	-	01(2.3%)
HELLP Syndrome	01(3.8%)	-	01(2.3%)
Acid Ingestion	-	01(6.25%)	01(2.3%)

Table 2: Indications of Elective Tracheostomy among Males and Females

Indications	Males (24 Patients) (57.1%)	Females (18 Patients) (42.8%)	N=42
GBS	13 (54.1%)	07 (38.8%)	20 (47.6%)
M.Encephalitis	04 (16.6%)	03(16.6%)	07(16.6%)
Tetanus	03(12.5%)	03(16.6%)	06(14.2%)
CVA	02(8.3%)	-	02(4.7%)
TBI	02(8.3%)	-	02(4.7%)
PPD	-	02(11.1%)	02(4.7%)
M.Gravis	-	01(5.5%)	01(2.3%)
Acid Ingestion	-	01(5.5%)	01(2.3%)
HELLP Syndrome	-	01(5.5%)	01(2.3%)

Graph 1: Relation of pattern of weaning and mode of Decannulation of TT with the day when elective tracheostomy done in the patients having traumatic brain injury (TBI) and cerebrovascular accident (CVA).



DISCUSSION:

The study focused on important clinical pathological indications of prolonged mechanical ventilation with tracheostomy for the patients coming to the settings of our hospital. In this study the neuromuscular paralysis turns out to be the commonest cause leading to prolonged mechanical ventilation and tracheostomy. There is paucity of work done on finding out the incidence and prevalence of different causative diseases for which patients undergo tracheostomy to continue prolonged mechanical ventilation. Generally due to heavy traumatic causalities coming to tertiary care hospitals, head injuries with coma are thought to be the leading indications for prolonged mechanical ventilation but in this study we observed neuroparalytic causes to remain on the top of the list during past two years and revealed Gullain Barre Syndrome (GBS) as the commonest medical condition responsible (47.6%) whereas the head trauma / Traumatic Brain Injury (TBI) was seen in 2 patients (4.7%), and turned out to be the only non surgical traumatic cause for putting the patients on prolonged mechanical ventilation with elective tracheotomy. Padhi and colleagues in their study revealed 50% of the patients requiring elective tracheostomy for prolonged ventilation were of traumatic brain injury(TBI)[2]. Datta et.al. in their study of 50 tracheostomies during two years found 2% cases of GBS[3]. Francois and Christian in their retrospective trial on critically ill patients of ICU found that the most frequent indication of tracheostomy was forthe prolonged mechanical ventilation[12].

In our study 57% were male patients & 43% were female patients. Datta et.al. in their study described the gender distribution as 80% of males & 20% of females[3]. Almost every patient requiring prolonged mechanical ventilation needs replacement of orotracheal intubation with tracheostomy tube. Boubaker et.al. in their retrospective comparative analysis found that replacing tracheostomy tube in ICU patients for prolonged ventilation carried

benefits of decreased ventilator induced lung complication but unchanged hospital stay and mortality[13]. In another cohort study conducted by Christophe and colleagues published in 2007 revealed no added benefit of elective tracheostomy among ICU patients in terms of disease mortality[4].

In our study on 42 ICU patients requiring tracheostomy for prolonged ventilation, there were 26 adult patients (62%) and 16 were children (38%). Some studies have been conducted exclusively on children and infants who underwent tracheostomies. In Agha Khan University Hospital Karachi Pakistan, Prem Kumar et.al. did a retrospective study on the children requiring elective tracheostomy for mechanical ventilation and mentioned that during the 5 years of observational study 2.2% of all children admitted in ICU needed elective tracheostomy with male predominance (60%)[11]. Whereas in our study out of total 16 children who underwent tracheostomy, 14 were male (87.5%). Considerable work has been done in the world on the timing of tracheostomy in patients on prolonged mechanical ventilation. The timing is counted from the day one of the orotracheal intubation and mechanical ventilation. In our study; 95.2 % of the patients had tracheotomy between 7-10th day with mean of 9th day. These patients had successful early weaning from mechanical ventilation and decannulation of tracheostomy. 4.7 % of the patients who were operated late (20th& 25th day) for tracheostomy had to suffer delayed weaning and failed decannulation of tracheostomy tubeat the time of discharge from ICU. Failed decannulation was due to subglottic stenosis. Researchers have argued the benefits of early tracheostomy in mechanically ventilated patients and mentioned the depending factors like nature of disease and selection of patients.Charles has mentioned that the decision of early tracheostomy in mechanically ventilated patients should be individualized, however traumatized patients especially with head injury / TBI can be benefited more from early tracheostomy[5]. He also advocated that the tracheostomy should be within 7 days of intubation[5]. Julian and colleagues in their randomized pilot trial have found that early tracheostomy in stroke related patients remained feasible and safe[8]. Van Der et.al. in a retrospective subgroup analysis found early weaning of 31 neurological / neurosurgical patients from ventilator with early tracheostomy as compared to the other subgroup[14].

Schauer and colleagues in their non randomized trial mentioned early tracheostomy with greater benefit in terms of duration of mechanical ventilation and hospital stay[15]. Aissaoui et al in a retrospective comparative analysis have found significantly better outcome in a group of patients who had tracheostomy before day 7 as compared to the other group where patients had tracheostomy after day 7[16].

A retrospective study of 531 mechanically ventilated patients by Arabi and colleagues found increased duration of mechanical ventilation and hospital stay associated with the timing of tracheostomy[17]. A meta analysis of 6 randomized controlled trials on 406 adult patients in 2005 found significant reduction of mechanical ventilation with early tracheostomy (mean 8.5 days)[18]. On the contrary Barquist et al in their prospective trials on traumatized patients did not find significant difference in the outcome of mechanically ventilated patients who had tracheostomy on day 8 as compared to those who had tracheostomy on 28th day[19]. Heidler and colleagues in their prospective multicentric study from 2014 to 2016 on 831 neurologically ill tracheostomized weaned patients found significantly negatively associated predictors with increasing age for early decannulation[20]. A study including case reports by Mitaka found facilitated weaning from prolonged mechanical ventilation if high flow oxygen was delivered through tracheostomy showing the enhanced benefit of doing tracheostomy in such patients requiring prolonged mechanical ventilation[21]. Likewise regarding the timing of tracheostomy Khammas and Dawood in their comparative analytical study described the clinical outcomes of early and late tracheostomy in the patients on prolonged mechanical ventilation. They found notable benefits like early weaning, lesser sedation and low risk of ventilation associated pneumonia in the patients who had early tracheostomy (within 1-10 days) than in those who had late tracheostomy (11-21 days) [22]. Yasir-ud-Din Hoti and colleagues studied early versus late tracheostomy in the patients of severe head injury and found early tracheostomy more beneficial in terms of ICU stay and mortality[23]. This study was carried out and published in Pakistan. Another local study conducted by Fazal and colleagues in 2018 assessing the secondary brain injury in the patients of severe head injury having early / late tracheostomy found increased morbidity and mortality in group of patients having late tracheostomy[24]. Amir Sabih Hydri et.al. studied the patterns of weaning and decannulation in the patients of ICU having surgical tracheostomy and interestingly found no prognostic dependence upon timing of tracheostomy but rather on underlying causative disease[25].

The limitations of our study were the small sample size, lack of detailed assessment on tracheostomy induced and mechanical ventilation associated complications in ICU patients due to its retrospective nature of the study design. It is recommended that large sample size study will be conducted to assess such complications like stomal injuries, tracheal ring injuries, pneumothorax, stomal stenosis, vascular erosions, nerve trauma, bleeding, infection and mechanical ventilation associated Pneumonia. Furthermore the preferred technique of doing tracheostomy and the place / venue of procedure are also the points of debate and question. Percutaneous dilatation tracheostomy on bed side in Intensive care unit has been advocated in some centers of the world.[25]

Hence wherever done and by any method adopted, tracheostomy should be performed as early as possible in the patients requiring prolonged mechanical ventilation.

CONCLUSION:

Different medical and surgical causes / indications were present in the patients requiring tracheostomy for prolonged mechanical ventilation. Neuroparalytic diseases more frequent in patients, with increasing trends among male adult patients.

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019070

Comparison of Allopurinol And Febuxostat in Asymptomatic Hyperuricemic Patients and their Impact on Serum Creatinine

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ABSTRACT

Objective: To determine the effect of Allopurinol & Febuxostat for the treatment of hyperuricemic patients & its influence on renal function by measuring serum creatinine level.

Study Design & setting: The clinical trial was conducted at Dr. Ruth K M Pfau Civil Hospital, Karachi, during the period of September 2018 to March 2019

Methodology: 60 patients with sUA > 6.8 mg/dl were registered. A detailed history was taken, patient's baseline serum Uric Acid (sUA) & serum Creatinine were measured. Patients were divided into two groups to receive Allopurinol, 300 mg & Febuxostat 80 mg, daily for 90-days. The blood parameters were repeated at day 30 and 90.

Results: Group-A (Allopurinol treated patients) baseline uric acid changed from mean 8.79 ± 0.98 mg/dl to 6.40 ± 0.86 mg/dl at day 90. In Group-B (Febuxostat treated patients) sUA baseline mean changed from 8.85 ± 0.97 mg/dl to 5.96 ± 0.68 mg/dl. Mean difference ± SD change of serum uric acid in Group-A was 2.39 ± 1.15 mg/dl and with Group-B it was 2.90 ± 0.87 mg/dl. Mean Serum Creatinine in Group-A changed from 1.54 ± 0.39 mg/dl to mean 1.48 ± 0.40 mg/dl compared with Group-B where it changed from 1.42 ± 0.30 mg/dl to 1.45 ± 0.31 mg/dl at day-90. Mean difference ± SD of serum Creatinine in Group-A was 0.11 ± 0.25 mg/dl & in Group-B it was, 0.03 ± 0.15 mg/dl. The above changes were statistically non-significant with p-value of 0.144.

Conclusion: Allopurinol and Febuxostat treatment resulted in improvement of serum Uric Acid levels while maintaining their renal function.

Key words: Allopurinol, Febuxostat, Serum uric acid, Serum creatinine.

INTRODUCTION:

Recent data have shown that hyperuricemia and gout are increasing worldwide. Since the last 40-years there has been a continuous rise in the incidence of hyperuricemic population around the world[1]. The international prevalence rate of hyperuricemia is 0.3% with a 90% male predominance, while 10 to 20% of patients exhibit a family history.[2]

Hyperuricemic patients present with a serum urate concentration above 6.8 mg/dL at which crystals are retained, cause severe damage to joint structures and are associated with poor kidney and cardiovascular outcomes [3].

The intrinsic sources of uric acid are degradation of purines by xanthine oxidase in the liver, intestine & muscles, while extrinsic sources are fatty meat, organ meat, and seafood [4].

Approximately 70% of daily production of urate is eliminated by the kidneys, and the remaining is expelled in the feces. However, the gastrointestinal passage of urate tries to overcome the reduced excretion by the kidneys during renal failure [5].

It seems that there is a close association between creatinine and uric acid synthesis. Uric acid is known to cause endothelial dysfunction, vascular smooth muscle cell proliferation, increased IL-6 synthesis, and impairment of nitric oxide production, all of which may contribute to the progression of chronic kidney disease.[6]

Uric acid may be associated with chronic kidney diseases through several mechanisms, direct renal toxicity, and hyperuricemia exacerbating other risk factors for kidney disease or it may be a marker of the severity of other risk factors, like diabetes and the metabolic syndrome [7].

Allopurinol, a xanthine oxidase inhibitor, is given orally and a commonly applied drug in hyperuricemia treatment, owing to its efficacy and good tolerability. Allopurinol is quickly oxidized by XO to hypoxanthine and xanthine, respectively. Allopurinol at low concentrations is competitive

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Received: 01-07-2019
Accepted: 03-12-2019

inhibitor and at higher concentrations is a noncompetitive inhibitor of xanthine oxidase enzyme. Allopurinol, as an antioxidant, scavenge free radicals such as hydroxyl radical and superoxide anion. Therapeutic applications, later first Phase-I human studies were carried out, following several years of laboratory studies [8].

Febuxostat, also a xanthine oxidase inhibitor, is a selective, non-purine derivative that was approved by the FDA in 2009 for its prolonged duration of action. It's efficacy in hyperuricemia and gout with potent urate lowering properties are documented.[9]

Febuxostat is metabolized by microsomal enzyme system in the liver, either actively oxidized and produces inactive acylglucuronide metabolites. Kidney excretes more or less 50% of the administered Febuxostat and only 10% as unchanged form of drug. Allopurinol hypersensitivity syndrome (AHS) is a rare but potentially serious risk for 2–8% of patients[10]. The rationale of therapy was to treat hyperuricemia with therapeutic doses of Allopurinol 300 mg/day & Febuxostat 80 mg/day, hoping to reduce the serum uric acid over long term, prevent relapses and have a beneficial impact on renal function by measuring serum creatinine levels.

METHODOLOGY

The study approved from BASR & ERB of Hamdard University, was conducted at Medical OPD, Dr. Ruth K M Pfau Civil Hospital, Karachi. Patients of either sex, ages varying from 38 to 69 years, having a serum uric acid concentration > 6.8 mg/dl and fulfilling the inclusion and exclusion criteria were registered after obtaining an informed and written consent. All available patients who met the study inclusion & exclusion criteria were included in this analysis.

Seventy [70] patients from Medical OPD were interviewed during the period of six months from Sept 2018 to March 2019; of these sixty patients were registered and divided into two groups, A & B, each having 35 patients. All patient data was entered in the designed pro forma. During follow up 10 patients, 5 from each group, dropped out due to irregularity in visits and poor adherence to drug.Group-A, was treated by Allopurinol (Zyloric) 300 mg once daily for 90 days Group-B, was treated by Febuxostat (Go-Uric) 80 mg daily for 90 days.

Patient details about serum uric acid & serum creatinine were recorded from baseline to day 90 in case recording file (CRF). All collected data of scheduled visits was entered for final statistical analysis.

Data was collected and processed on SPSS version 22. Results were described as percentages. One sample t-test paired sample test and Chi-square were used to determine the mean and standard deviation. P value <0.05 was taken as significant.

RESULTS:

In Group-A thirty registered patients completed the study duration with Allopurinol treatment for 90-days, with the following baseline characteristics; males 22 (73.3%), mean age 57.60 + 6.11 years (range 45 to 68 years), mean body weight 63.27 + 5.74 kg, 16 (53.3%) smokers, mean serum uric acid 8.79 + 0.98 mg/dL, mean serum creatinine 1.54 + 0.39 mg/dL. [Table-1] Group-B registered thirty patients had the following baseline characteristics; 21 (70%) male, 9 (30%) females mean age 54.30 + 8.66 years (range 40 years to 69 years), mean body weight 65.03 + 7.22 kg, 13 (43.3%) smokers, mean serum uric acid 8.85 + 0.97 mg/dl & mean creatinine 1.48 + 0.40 mg/dl. [Table-1]

Group-A (Allopurinol 300 mg/daily): The change in mean serum uric acid from day-0 to day-90 was 8.79 + 0.98 mg/dL to 6.40 ± 0.86 md/dl [p value < 0.001, with percentage change of 27%, mean serum creatinine 1.54 ± 0.39 mg/dl to 1.42 ± 0.30 mg/dl [p value < 0.019], with percentage change of 8%. [Table-2]

Group-B (Febuxostat 80 mg/daily): The change in mean serum uric acid from day-0 to day-90 was 8.85 ± 0.97 mg/dl to 5.96 ± 0.68 mg/dl [p value < 0.001], percentage change was 33%, mean serum creatinine 1.48 ± 0.40 mg/dl to 1.45 ± 0.31 mg/dl [p value < 0.258], with percentage change of 2%. [Table -2] Mean difference ± SD for change of serum uric acid in Group-A was 2.39 ± 1.15 mg/dl with Group-B mean was 2.90 ± 0.87 mg/dl. Regarding this decrease there was no significant statistical difference between Allopurinol & Febuxostat with p-value 0.061. Mean difference ± SD, for change of serum Creatinine in Group-A was 0.11 ± 025 mg/dl. & Group-B, 0.03 ± 0.15 mg/dl. There was no significant statistical difference between Allopurinol & Febuxostat with p-value 0.144. Table-3

Adverse reactions in the study Group-A were reported in 9 out of 30 patients and in Group-B, 4 out of 30 patients. [Table-4]

Table-1: Comparison of baseline characteristics of group-A & group-B in hyperuricemic patients

	Group-A n=30	Group-B n=30
GENDER		
• **Female**	8 (26.7%)	9 (30%)
• **Male**	22 (73.3%)	21 (70%)
Age in years (Mean+SD)	57.60 ± 6.11	54.30 ± 8.66
Smokers	16 (53.3%)	13 (43.3%)
Non-Smokers	14 (46.7%)	17 (56.7%)
Body Weight Kg	63.27 ± 5.74	65.03 ± 7.22
Serum Uric Acid mg/dl	8.79 ± 0.98	8.85 ± 0.97
Serum Creatinine mg/dl	1.54 ± 0.39	1.48 ± 0.40

Group- A: Allopurinol 300 mg once daily, Group-B: Tab Febuxostat 80 mg daily, n= Number of Patients

Table-2
Comparison of serum uric acid & serum creatinine between Group-A & Group-B in hyperuricemic patients. (Day -0 and Day -90)

Group A (Allopurinol)	Day	Mean ± SD	P-value*
Serum Uric acid mg/dl	Base line (Day – 0)	8.79 ± 0.98	< 0.001**
	After treatment (Day – 90)	6.40 ± 0.86	
	Percentage Change	27%	
Group B (Febuxostat)			
Serum Uric acid mg/dl	Base line (Day – 0)	8.85 ± 0.97	< 0.001**
	After treatment (Day – 90)	5.96 ± 0.68	
	Percentage Change	33%	

Group A (Allopurinol)	Day	Mean ± SD	P-value*
Serum Creatinine mg/dl	Base line (Day – 0)	1.54 ± 0.39	< 0.001**
	After treatment (Day – 90)	1.42 ± 0.30	
	Percentage Change	8%	
Group B (Febuxostat)			
Serum Creatinine mg/dl	Base line (Day – 0)	1.48 ± 0.40	< 0.001**
	After treatment (Day – 90)	1.45 ± 0.31	
	Percentage Change	2%	

* Dependent or Paired t test
** Significant

Table-3 Comparison group A & B for Change in Serum Uric Acid level (Day -0 and Day -90)

Group A & B	Mean Difference ± SD	P-value*
Group A	2.39 ± 1.15	0.061
Group B	2.90 ± 0.87	

Comparison group A & B for Change in Serum Creatinine level

Group A & B	Mean Difference ± SD	P-value*
Group A	0.11 ± 0.25	0.144
Group B	0.03 ± 0.15	

Table-4 Adverse Effects Of Allopurinol & Febuxostst

Adverse effect of drugs	Response	Group-A Allopurinol 30mg0		Group-B Febuxostat 80mg	
		No.	%	No.	%
Abdominal pain	Yes	03	10	00	00
	No	27	90	30	100
Palpitation	Yes	02	6.7	00	00
	No	28	93.3	30	100
Hematuria	Yes	02	6.7	01	3.3
	No	28	93.3	29	96.7
Hypersensitivity	Yes	02	6.7	00	00
	No	28	93.3	30	100
Numbness	Yes	00	00	01	3.3
	No	30	100	29	96.7
Headache	Yes	00	00	01	3.3
	No	30	100	29	96.7
Vomiting	Yes	00	00	01	3.3
	No	30	100	29	96.7
Fever	Yes	00	00	00	00
	No	30	100	30	100
Fatigue	Yes	00	00	00	00
	No	30	100	30	100

DISCUSSION:

Hyperuricemia prevalence not only is reported in developed countries but evidence is also coming from the low and middle-income countries and incidences are continuously rising. Evaluation of an epidemiological study conducted on healthy volunteers for over seven years showed that raised serum uric acid increases the risk for new outbreaks of kidney function impairment. [11]

The prevalence of hyperuricemia is 1–4%. In European countries, with male predominance 3–6% & 1–2%in female, as the age advances prevalence rises to 10% & 6% respectively in both sexes. Yearly incidence is 2.68 per 1000 persons, being 2-6 times greater in males.[12]

Hyperuricemia pathophysiology is not clearly known, imbalance of breakdown of purines and uric acid excretion is answerable to its action. Most cases of hyperuricemia present clinically because of faulty urate excretion. Raised serum uric acid is now established as a potential risk factor for developing number of disturbances. Hyperuricemia in the initial days was recognized as gout, but now it is considered as a separate entity and responsible for number of metabolic and hemodynamic abnormalities.[13]

The present study demonstrates that with Allopurinol treatment, the serum uric acid reduced from a mean of 8.79 + 0.98 mg/dl to a mean of 6.40 + 0.86 mg/dl on day 90, total percentage change being 27% and mean serum creatinine reduced from a mean of 1.54 ± 0.39 mg/dl to a mean of 1.42 ± 0.30 mg/dl, percentage change being 8%. These findings are in agreement with the study conducted by Becker, 2005.[14]

In renal dysfunctions a better option is to start with the minimum dose. A reduced initial target dosage in renal impairment is still defended but studies suggest that when unable to obtain desired effects, the dosage may be increased above the present guidelines. In our study, the renal function

assessment was within normal limits and Allopurinol therapy did not influence the serum Creatinine level; these findings are in agreement with those of 2007.[15]

In a clinical trial conducted by Whelton 2011 in which Febuxostat was used, significant change in serum creatinine was found, which is in agreement with our study [16]. Similarly, a study conducted by Kanbay et al showed that treatment with Allopurinol led to decrease in serum creatinine after 3 months [17].

Study conducted by Perez-Ruiz, 2000 validated that higher doses of Allopurinol are more effective in decreasing concentration of uric acid, but Allopurinol 300 mg adequately decreased uric acid concentration without influencing the renal functions; these results matched with our study[18].

Use of Febuxostat by Grassi for short period of 1 to 6 months duration significantly reduced the serum uric acid concentrations. Our study findings are in agreement with Grassi.[19].

Becker[9], conducted clinical trial of 52 weeks duration using Febuxostat and Allopurinol, in which serum uric acid was reduced to 6.0 mg/dL during the first 3 months; these findings matched with our results in the reduction of serum uric acid at day 90 with the change being more marked with Febuxostat than Allopurinol.

Our study also agrees with Borghi, 2016 [20] who reported, that in hyperuricemia, Febuxostat is a suitable option and should be considered as a first line drug as, it has provided safe and efficient effects in clinical studies.

In a study of 28-weeks by Schumacher[21], conducted with different doses, Febuxostat more adequately reduced and maintained serum urate levels < 6.0 mg/dl than Allopurinol, at doses 300 & 100 mg or placebo in hyperuricemic patients and gout, with mild to moderate renal dysfunction. In our study, Allopurinol 300 mg/day & Febuxostat 80 mg/day productively decreased serum uric acid without any disturbance of renal function with better effects reported in Febuxostat group of patients.

A clinical study conducted in patients with hyperuricemia and gout by Michael in 2005, using Febuxostat and Allopurinol showed reduction in serum uric acid levels[22]. In our study Febuxostat 80 mg, daily more effectively reduced the serum uric acid concentration that is 39%, compared with Allopurinol 300 mg daily that showed 27% reduction.

Kamatani[23] conducted a comparative study of Allopurinol & Febuxostat in doses 200 mg & 40 mg/day respectively for the period of 44 days and showed that Febuxostat at 40 mg/daily demonstrated more potent hypouricemic effects than Allopurinol at 200 mg/day. In our study Febuxostat 80mg/day & Allopurinol 300mg/day for 90 days demonstrated that Febuxostat is more potent than Allopurinol in hyperuricemia.

Similarly, the CONFIRMS trial conducted by Becker [24] and using Febuxostat significantly reduced serum uric acid levels in a 6-month study of 2269 patients with normal renal function.

Frampton[25] pointed that earlier studies have identified cardiovascular toxicities with Febuxostat; ongoing trials are in progress to identify the cardiovascular safety of Febuxostat versus Allopurinol. In our 90-day study sixty hyperuricemic patients were monitored for drug safety. We observed no serious adverse events related to drugs used during the study period except for abdominal pain, palpitations and hematuria in patients on Allopurinol, all of which were easily self-controlled.

Study conducted for short duration and limited number of patients, poor adherence, non-compliance, illiteracy and poor socio-economic issues are some important limiting factors.

CONCLUSION:

Febuxostat was superior to Allopurinol in reducing serum uric acid as well as reducing serum creatinine in asymptomatic hyperuricemia patients. Furthermore, no serious adverse events were seen in our study proving the safety of the drugs.

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019062

Evaluation of Mandibular Ridge Lingual Concavity Using Cone Beam Computed Tomography

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ABSTRACT

Objective: To evaluate the type and depth of lingual concavity in posterior mandible using pre-treatment CBCT (Cone Beam Computed Tomography) images for dental implants.

Study Design and Setting: A cross-sectional study was designed and conducted on pre-treatment CBCT scans of 75 patients at Armed Forces Institute of Dentistry, Rawalpindi, Pakistan from February 2018 to November 2018.

Methodology: Pre-treatment CBCT scans of 75 patients were selected and following parameters were measured: type of ridge (undercut, parallel, convex), ridge width, ridge height, depth of lingual concavity, concavity angle, and location of the undercut. Data was analyzed using SPSS version .24. Post-stratification Mann-Whitney U test was used for effect modifiers, while Kruskal-Wallis test was used to compare study parameters between groups. P value <0.05 was taken as significant.

Results: A mean concavity depth of 1.17±1.40 mm was observed while majority (46.7%) of the CBCT images presented with undercut type ridge. No significant difference was observed between males and females for any study parameter.

Conclusion: Undercut ridges were frequently observed, posing a threat of lingual perforation during implant placement. Pre-operative assessment of implant site using CBCT can serve as a reliable method to avoid such complications.

Keywords: Alveolar Ridge, Cone beam computed tomography, Dental Implant, Mandible.

INTRODUCTION:

In contemporary dentistry, the primary goal is to restore the patient's function, esthetics, comfort, speech and optimum oral health.[1] In consideration of these goals, dental implants have become a significant factor and have proved to be the closest equivalent in replacement of natural teeth. Success and outweighing of dental implants to other viable treatment options is mainly due to their superior biocompatibility, stability, maintenance of bone, strength and survival.[2]

However, in spite of their higher survival rates, certain factors such as failure in diagnosis and proper treatment planning may lead to failure of implants. These factors therefore must be taken into consideration prior to placement of implants. Surgical complications during implant placement is one of the factor that cannot be underestimated.[3] McDermott et.al. in a retrospective study on 677 patients reported an overall higher frequency of surgical complications associated with implant placement.[4] Implant angulation generally follows the long axis of occlusal forces in the posterior region of the dental arch.[5] This is because bone can resist compression forces better than tensile or shear stresses.[6] An axially loaded implant can direct more compressive than tensile or shear forces on bone. In addition, better stress/strain distribution is possible when implants are placed along the axis of loading with multiple areas of cortical contact.[7]

One of the main surgical accident that can occur is the perforation of osseous boundaries during the placement procedure especially in the posterior lingual concavity.[8] This can lead to numerous complications including infection, inflammation, damage to other vital structures and eventually implant loss.[9] The cause of perforation in posterior mandible is the presence of lingual concavity which is due to the presence of submandibular and sublingual salivary gland.[10]

Mandible morphology and contour has previously been described by Zarb but buccolingual dimensions and concavities have not been covered in the classification.[11] Quirynen et.al. have conducted a cross-sectional study on inter-foraminal morphology and presence of lingual concavity.[12] Chan et.al. measured the depth of this concavity in the mandibular molar area and classified the ridges

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Received: 12-06-2019
Accepted: 25-11-2019

according to their morphology as being undercut, parallel or convex.[8] Familiarity with various vital structures in the region of prospective implant placement, along with thorough treatment planning, is the guaranteed way to avoid surgical complications.[13,14] Lekholm&Zarb described five stages of jaw bone resorption, describing them from least to most and then used this classification in treatment planning of implants.[15] Their area of interest was volume alterations of the residual ridge after extraction of tooth. Later, the ridge morphology in the inter-foraminal region was discussed thoroughly and the incidence of lingual undercut was labelled as "potential risk" of intra-operative complications.[12,16] However, for the posterior mandibular, data about lingual concavity is apparently infrequent. Such concavity can be detected by many methods each having own limitations. Nowadays, best available modality is cone-beam computed tomography (CBCT) as it has comparatively less radiation exposure and allows three-dimensional visualization.[8,17] An accurate radiograph serves as a useful guide for surgeon, as it helps determine fixture size and informs about ridge concavities.[18]

The aim of this study was to evaluate the type and depth of lingual concavity in posterior mandible in the local population using pre-treatment CBCT images for dental implants.

METHODOLOGY:

A cross-sectional study was designed and conducted at Armed Forces Institute of Dentistry, Rawalpindi, Pakistan from February 2018 to November 2018. Prior approval from Institutional Ethics Committee was taken. Based on previously published data,19 keeping confidence level (1-α) at 95%, absolute precision (d) at 0.2, population mean (μ) at 2.4, population standard deviation (σ) at 1.1, a total sample size of 75 was calculated. CBCT scans of patients taken using a NewTomVGi CBCT machine (QR s.r.l, Italy) for the purpose of pre-implant planning were selected. Informed consent was taken from the selected subjects to use their data anonymously for research. Scans of both male and female patients, aged 20-60 years, taken three months after extraction of mandibular first molar were included. The area of interest was edentulous ridge in the region of mandibular first molar, where the first molar itself should be absent but not the second premolar, with adequate vertical bone height in the area (12 mm between ridge crest and upper border of IAN canal) and bone width > 4 mm. Patients with bony pathologies were excluded as were CBCT images with artifacts that made identification of reference points difficult.

Figure 1 illustrates different measurements taken of mandibular cross-sectional morphology. On a given cross section under study, the region above the horizontal line X (2 mm above upper border of IAN canal) was evaluated, as the recommended implant position is 1.5 mm above IAN. Buccolingual width of the ridge 2 mm superior to IAN (Wa) and 2 mm inferior to the level of alveolar crest (Wb) was measured. Most prominent point on lingual aspect of the ridge was labelled as point A. Point B was intersection of line X and lingual plate. Distance between residual ridge crest and line X (Va) was measured. Three types of cross-sectional mandibular ridge morphology were determined. Undercut (U) ridge type indicated a ridge with a narrow base and wider crest buccolingually with a prominent point A on lingual aspect, when studied in cross section. Parallel (P) ridge type had no obvious undercut with more or less parallel buccal and lingual plates. Convex (C) type ridge had no undercut with wider base and narrower crest. Prevalence of each ridge type was calculated. Concavity angle was measured in degrees, by determining the angle between lines X and Y. Horizontal distance between point A and point B was labelled as linear concavity depth. Greater concavity had greater angle with lesser depth. Vertical distances from alveolar crest to point A (Vb) and inferior border of mandible to point A (Vc) were also measured to determine the vertical location of concavity. Data was analyzed using SPSS version 24. Data was not normally distributed, hence non-parametric tests were selected. Descriptive statistics were calculated. Post-stratification Mann-Whitney U test was used for effect modifiers such as gender, while Kruskal-Wallis test was used to compare study parameters between groups. $P<0.05$ was taken as significant.

RESULTS:

Of the 75 selected patients, 36 (48%) were male and 39 (52%) were female. Mean bone width (Wa) was found to be 7.15±1.62 mm while a mean concavity depth of 1.17±1.40 mm was observed. Table 1 illustrates the mean and standard deviations of all study parameters. Majority (46.7%) of the subjects presented with undercut type ridge. Figure 2 highlights the frequency of different types of ridges observed. No significant difference was observed between males and females for any study parameter (Table 2). Table 3 highlights the difference in study parameters between different ridge types.

DISCUSSION:

In addition to ridge height and width, lingual concavity depth and angle are important factors to be considered in implant placement. They help to place and align the drill properly during osteotomy.[20] In the present study, mean mandibular lingual concavity depth was 1.17±1.40 mm

Table 1: Descriptive statistics of study parameters (N=75)

Study Parameter	Mean± SD	Median
Bone width Wa	7.15±1.62	6.9
Bone width Wb	10.97±1.19	10.8
Bone Height Va	14.36±2.54	14.7
Concavity angle	31.78±35.97	60.2
Concavity depth	1.17±1.40	1.2
Vertical undercut position Vb	3.04±3.68	9.9
Vertical undercut position Vc	8.42±9.54	10.5

Table 2: Comparison of study parameters between Males and Females

Study Parameter	Gender	Mean Rank	P value (Mann-Whitney U test)
Bone width Wa	Male Female	38.33 37.69	.898
Bone width Wb	Male Female	39.65 36.47	.527
Bone Height Va	Male Female	37.38 38.58	.811
Concavity angle	Male Female	34.64 41.10	.163
Concavity depth	Male Female	36.33 39.54	.489
Vertical undercut position Vb	Male Female	34.44 41.28	.139
Vertical undercut position Vc	Male Female	36.97 38.95	.670

Table 3: Comparison of study statistics between subjects with different ridge types

Parameter	Ridge Type	N	Mean Rank	P value (Kruskal-Wallis Test)
Bone Width Wa	Undercut Parallel Convex Total	35 16 24 75	57.77 28.28 15.65	<.001
Bone Width Wb	Undercut Parallel Convex Total	35 16 24 75	20.26 46.59 58.15	<.001
Bone Height Va	Undercut Parallel Convex Total	35 16 24 75	36.17 39.38 39.75	0.792
Concavity Angle	Undercut Parallel Convex Total	35 16 24 75	58.00 20.50 20.50	<.001
Concavity Depth	Undercut Parallel Convex Total	35 16 24 75	58.00 20.50 20.50	<.001
Vertical Undercut Position Vb	Undercut Parallel Convex Total	35 16 24 75	58.00 20.50 20.50	<.001
Vertical Undercut Position Vc	Undercut Parallel Convex Total	35 16 24 75	58.00 20.50 20.50	<.001

(median: 1.2 mm).Similar results have been reported by Panjnoush et.al. [21] who found a mean lingual concavity depth of 1.3±1.54 mm, and by Kamburoglu et.al. who also reported a mean concavity depth of 1.3 mm.[22] However, the results of the present study differ from those of Chan et.al. . who reported a mean concavity depth of 2.4 mm.[8] Parnia et.al. also reported a greater mean concavity depth

Figure 1: Different measurements taken of mandibular cross-sectional morphology

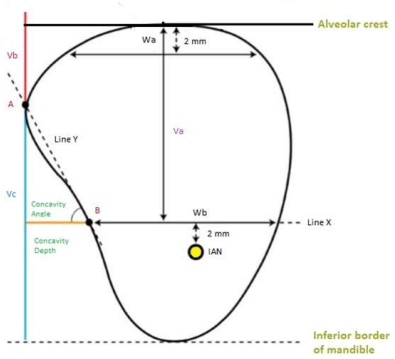
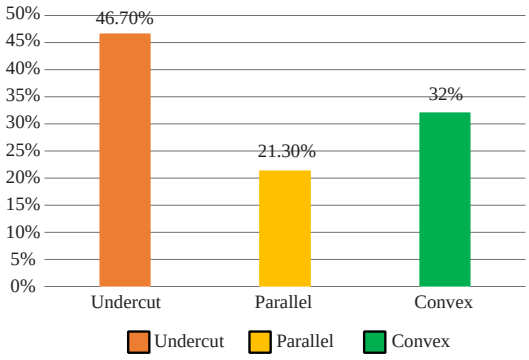


Figure 2: Types of mandibular ridges



of 2.6±0.85 mm.[20] These differences may be attributed to a difference in measurement methods as well as to differences in ethnicity of the study population.

In the present study, 56% (n=42) of subjects showed mandibular lingual concavity depth more than zero , which was lower than Chan et.al. study (66%)and Nickenig et.al. (68%).8, 10 In the study by Chan et.al.[8] subjects were classified into three types C (convex), P (parallel), U (undercut) according to ridge morphology, where a higher frequency (66%) of undercut ridges was encountered.The same morphologic classification was used in this current study and undercut ridges were found to be more frequent (46.7%, n=35).

No significant difference was observed between males and females in term of ridge morphology in this study. The findings are endorsed by those of Chan et.al.[8] Salemi et.al.,[9] and Yoon et.al.[23] However, conflicting results have been reported by Zhang et.al. . who found a significant difference in mandibular width between males and females. The researchers measured the distance between external surface of buccal and lingual cortical plates, and this method of measurement is perhaps the reason for varying results.

Undercut ridges present an increased risk of lingual perforations during implant placement. The consequences of lingual plate perforation vary depending upon the site of the perforation. In anterior mandible, lingual perforation

can damage submental and sublingual arteries, resulting in massive, potentially fatal hemorrhage.[24] Apart from the submandibular gland and lymph nodes, the sub-mandibular space, on the contrary, is devoid of any vital structures. Lingual nerve can be damaged if the lingual plate is perforated above the mylohyoid ridge.[19] If implant is exposed in the oral cavity, persistent inflammation or infection may develop and can lead to more serious complications. Such infections although do not develop immediately, but their insidious nature requires careful prior treatment planning.

Conventionally, prospective implant sites have been assessed using periapical and panoramic radiographs. Since these techniques are two-dimensional, they fail to provide adequate accurate information about bone width i.e. the bucco-lingual dimension.[9] In contrast, CBCT offers benefits of low radiation exposure, high resolution and accuracy, relative cost-effectiveness and less technique sensitive.[1,17,20] As lingual concavity poses a serious risk of perforation during implant placement, it is prudent to use CBCT to assess mandibular ridge morphology, quality and quantity prior to implant surgery.[17] Such careful treatment planning can be instrumental in preventing intra- and post-operative complications.

CONCLUSION:

A mean concavity depth of 1.17±1.40 mm was found in the study sample. Of the three ridge types, undercut ridge had the highest frequency followed by convex and parallel. No significant association was found between any mandibular ridge morphological parameter and gender. Pre-operative assessment of implant site using CBCT can serve as a reliable method to avoid complications

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019072

Comparative Analysis of The Effects of Short-Term Metformin and Metformin-Insulin Combination on the Liver in Diabetes Wistar Rats

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ABSTRACT

Objective: To compare the effects of drugs (Metformin and combination) on weight, size and volume of liver in diabetic rats.

Study Design and Setting: This was an experimental comparative study conducted at Institute of Bio Medical Sciences (IBMS), Dow University of Health Sciences (DUHS), Ojha Campus, Karachi.

Methodology: The study was conducted on 40 albino wistar rats. Diabetic rats (n=20) were grouped into 2. One group was treated with metformin (n=10)while the other group with insulin-metformin combination (n=10) for 4 weeks. All the treated groups were compared with untreated diabetic killed (n=10). After a short period of 4 weeks, all the rats were sacrificed. Livers were isolated, weighed and grossly observed for significant changes. Absolute and mean percent liver weights as well as liver volumeof all rats were calculated.

Results: Data was analyzed by using GraphPad Prism version 5.0.Data for absolute/percent liver weight and liver volume was expressed as Mean ± SEM. The value obtained was analyzed by Two-way ANOVA followed by Bonferroni test wherever applicable.P-value of = 0.05 was considered as statistically significant.

Conclusion: The short-term metformin and insulin-metformin treatment doesn't effect liver weight and volume significantly and hence, their short-term use is beneficial in type 2 diabetes.

Key words: Diabetic rats, diabetes type 2, fatty liver ,insulin, liver volume, metformin

INTRODUCTION:

Diabetes is steadily increasing with an estimated increase from approximately 8.8 percent of global adult population in 2017 to almost 10 percent by the year 2045.It's estimated that the number of diabetic people will rise to 366 million in 2030.The estimated diabetics in the year 2000 is171 million.

Diabetes is a well-known chronic disorder affecting multiple organs and seriously affecting the quality of life. It can be classified into 2 types depending on the absolute or relative deficiency in insulin secretion. This will lead to a cascade of various pathological processes starting from deficient insulin secretion to insulin resistance IR. Uncontrolled diabetes can trigger lethal complications involving almost every organ of the body. Fatty liver disease observed in diabetes is classified as non-alcoholic fatty liver disease (NAFLD) which involves infiltration of hepatocytes with fat progressing slowly from a reversible steatosis to irreversible liver fibrosis and failure. Hepatic Steatosis (HS) is a reversible injury to hepatocytes causing accumulation of fat in the liver replacing functional liver cells. Approximately 78% diabetics suffer from steatohepatitis which is observable in the liver ultrasound of diabetics. NAFLD progresses silently in diabetics and is frequently overlooked.

Resistance of cells to insulin is the main underlying cause of both DM2 and NAFLD which triggers lipid-accumulation process. This further increase free fatty acid delivery to liver due to mobilization of the peripheral fat.Such histological changes in liver induce hepatic insulin resistance (HIR), further aggravating fat metabolism in liver. A strong association between HS and HIR has already been researched indicating an inverse relation between them; as the body sensitivity to insulin decreases and fat accumulation in liver increases.

Diabetes will remain the focus of research till the scientists discover complete and effective treatment for diabetes. Likewise, anti-diabetics would continue to be under evaluation for their maximum effectiveness and minimum

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Received: 09-07-2019
Accepted: 15-11-2019

side effects. Among anti-diabetics; Insulin and metformin remain frequently prescribed drugs for the clinicians because of their best results in maintaining blood glucose levels.[12] Both drugs are used as monotherapy as well as in combination. As compared to mono therapy, good results are observed with combination therapy as it keeps in check the liver enzymes as well as blood glucose levels. Insulin when used alone have harmful effects on liver while metformin have good results on liver and blood glucose.

Metformin is well-known for its effectiveness in diabetes type 2 and is proven to be safe as 1st line drug of treatment. The drug causes decreased glucose absorption in the gut and increase in hepatic glucogenesis leading to low blood glucose levels. Moreover, metformin also decreases insulin resistance (IR) by increasing insulin levels and glucose uptake in muscle and adipocytes, hence improving insulin action. The drug also has vital role in decreasing circulating lipids which could be a possible factor required for the management of abnormal liver enzymes and HS.

Keeping in view the above literature search, the present study was aimed to evaluate and compare the effects of drugs (Metformin and combination) on weight, size and volume of liver in diabetic rats.

METHODOLOGY:

This was an experimental comparative study. Total (n= 40) wistar rats were selected via random sampling. Experimental groups were divided into four; each having 10 rats:

Group A [Control]: (n=10); Group B [Diabetic]; (n=10); Group C [Metformin-treated diabetic rats] (n=10); Group D [Insulin metformin combination-treated diabetic rats](n=10). Each group was kept in a clear sided plastic cage under suitable room temperature, sunlight and ventilation. All rats were provided with appropriate diet and water ad libitum. Weekly observations of body weight of all rats were carried out via a digital scale till they were sacrificed. Metformin treated rats were given oral metformin in a dose of 200mg/kg/day while combination treated rats were given insulin in adose of 3U/kg/day intraperitoneally while metformin was used in the dose as mentioned previously.Anti-diabetic treatment was given for 4 weeks. Afterwards rats were carefully dissected as per standard protocol and liver was isolated. Liver volume of all rats (length x breadth x height) were calculated. Absolute liver weight (ALW), relative weight and percent liver weight (PLW) were noted. PLW was calculated using the formula: PLW=weight of liver/body weight x 100. Data for ALW/, PLW and liver volume were expressed as Mean ± SEM. Graph pad Prism software version 5.0 was used for analysis. ANOVA was applied on the study variables followed by Bonferroni test wherever applicable. P-value of = 0.05 was considered as statistically significant.

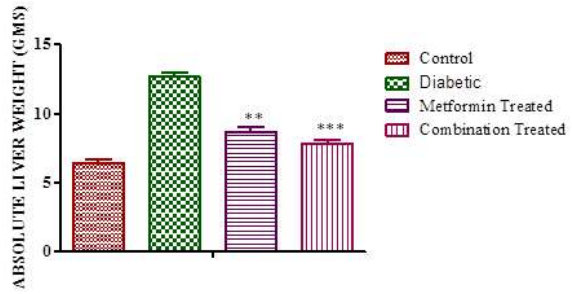
RESULTS:

Descriptive statistics of all study variables were mentioned in table 1. Group wise comparisons were expressed as mean ± SEM**.** Significant difference (P value < 0.01) in ALW was observed in rats that received metformin as compared to untreated group. The ALW was more significant (P value < 0.001) in combination treated groups (Graph I). Descriptive statistics revealed that short-term combination treatment has more effective role in reducing ALW as compared to metformin (Table I). However, no significant (P value >0.05) difference in PLW was observed in all treated groups (Group C and Group D)as compared to untreated and control group (Graph II). The liver volume was more significant (P value <0.001) in both Group C and Group D as compared to untreated group (Graph III).

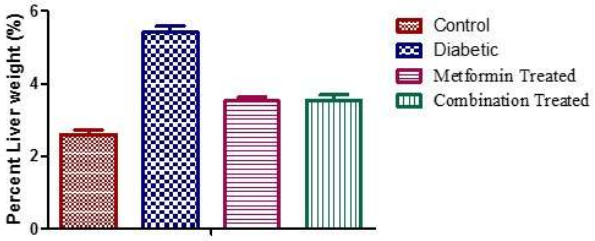
DISCUSSION:

Research innovation is under a great turmoil to explore the path of cure for numerous untreatable diseases. Diabetes type 2 is one of these diseases which can be controlled with medicines but cannot be treated. Hence, the disease will be in research limelight until the researchers discover its cure.

Graph I: Absolute Liver Weight in all Experimental groups



Graph II: Showing Percent Liver Weight in all Experimental groups



Graph III: Liver Volume in all Experimental groups

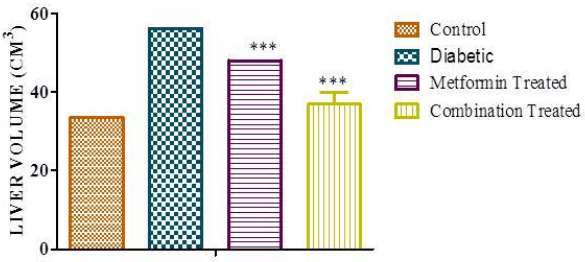


Table I: Absolute Liver Weight (ALW), Percent Liver Weight (PLW) And Liver Volume In Treated And Untreated Groups In Comparison To Control Group

GROUPS (n=40)	ALW GMS MEAN±SEM	PLW GMS MEAN±SEM	Liver volume CM^3 MEAN±SEM
GROUP A (control)	6.449±0.239	2.601±0.216	33.550 ± 0.000
GROUP B (untreated diabetic)	12.460±0.361	5.425±0.159	56.260 ± 0.000
GROUP C (metformin treated)	8.700±0.300	3.519±0.109	48.080 ± 0.000
GROUP D (insulin-metformin treated)	7.780± 0.317	3.544 ± 0.152	36.916 ± 3.080

Meanwhile its vital to explore effective medicines with minimum side effects. Metformin and its combination are widely used to control blood glucose levels. The current study is focused on analyzing their effects on absolute and percent weight of liver along with liver volume. Use of either metformin or in combination with insulin has reduced liver volume, absolute and percent liver fat significantly, but combination seems more effective. Also, metformin is widely used in Hepatic Steatosis (HS) of almost all etiologies and has effective results. The results of the study were in comparison with other studies. Findings of the study suggest that the short-term use of insulin metformin combination can be beneficial for diabetic patients and has less side effects on liver cells.

CONCLUSION:

The short-term use of metformin and metformin-insulin combination in diabetic wistar rats had produced beneficial effects on liver.

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019086

Effects of Virtual Rehabilitation and Constraint Induced Movement Therapy on Brain Derived Neurotrophic Factor Mediated Motor Improvement in Stroke Patients

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ABSTRACT

Objectives: To carry out a comparison between serum BDNF levels as well as enhancement in upper limb motor function in terms of gross movement, pinch, grip, primary grasp, pre and post intervention in the study and control groups.

Study design And Setting: It was a Randomized Control Study conducted from March 2015 to March 2016 at Holy Family Hospital Rawalpindi in collaboration with the Multidisciplinary research laboratory at Islamic International Medical College, Rawalpindi.

Methodology: In this study; forty stroke patients were randomly designated to either the study group or the control group. Upper limb activity capability which was quantified by Action Research Arm Test (ARAT) and serum Brain Derived Neurotrophic Factor (BDNF) was measured in both control and study group. The control group underwent traditional upper limb physiotherapy for 16 sessions. The study group underwent Constraint Induced Movement Therapy for the upper limb in combination with the use of motion capture video gaming technology for 16 sessions each of twenty minutes duration. Before and after completion of intervention sessions; ARAT and serum BDNF were measured and compared in both control and study groups.

Results: Serum BDNF levels was significantly improved in study group as compare to control group ($p<0.001$). ARAT showed significant improvement in study group participants as compare to control groups ($p<0.001$).

Conclusion: Virtual rehabilitation was an efficacious method for Neuroplastic enhancement in stroke patients.

Keywords: Action Research Arm Test, Brain Derived Neurotrophic Factor, Neuroplasticity, Stroke.

INTRODUCTION:

Stroke is the leading cause of debility and motor function impairment throughout the world affecting 350,000 individuals each year.[1] The prevalence of this debilitating disorder has surpassed 4.8% in Pakistan.[2] There are two chief defects that lie at the root of the etiology of stroke; one being "Throm boem bolism" of arterial vessels of the brain, and the other, disruption of the flow of blood in the cerebrovascular system. Stroke due to inadequate blood flow to the cerebral tissues claims 87% of the total head-count of stroke whereas stroke caused by cerebrovascular bleeding ("spontaneous intracerebral and subarachnoid hemorrhage") accounts for the rest.[3] Motor function debility is one of the main manifestations of stroke, being able to recover motor function (upper extremity motor function)after surviving the initial onslaught of the disease via physiotherapy has a resultant encouraging influence on upper limb motor activity, a consistent measure of which is the action research arm test (ARAT).[4]

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Received: 31-07-2019
Accepted: 25-11-2019

Neuronal growth and healing, formation of new neuronal connections, strengthening of protective mechanisms in nerve cells especially following brain damage caused by deprivation of adequate blood flow, and generalized improvement of neuronal health and vitality has been closely linked to a peptide based growth factor known as Brain-derived neurotrophic factor.[5] BDNF has been shown to reduce the degree of cerebral infarction and aid natural salvage of damaged nerve cells.[6]Re-establishment of motor function after stroke is known to rely on the formation of new axonal and dendritic connections and other inherent, damage-control modifications and mechanisms within the nervous system known as "neuro-plasticity".[7]Rehabilitative techniques that demand self-directed, goal oriented, dynamic and repeated movements have shown to result in better, "plasticity based" enhancement of neuronal health after damage incurred by stroke.[8]

Constraint-induced movement therapy is a technique of physical therapy in which the patient is made to constrain the unaffected limb and is forced to make use of the weakened

limb for the majority (90%) of the time that he/she is awake. This form of therapy also demands that the activities carried out by the patient should be goal oriented and task specific (like movement of the impaired arm), with gradually increasing intensity based on the patient's progress ; a type of conditioning of behavior known as "shaping".[9]

An emerging trend in the field of stroke rehabilitation that has gained attention in the recent years is "Virtual Rehabilitation" which essentially aims to cause structural and functional rewiring of the parts of the brain that are responsible for consolidation of memories, learning and motor function by stimulating the "mirror-neuron system".[10, 11, 12] "Nintendo Wii™" has been one of most widely used video-game technologies; as it is low-cost and user friendly. It requires that the player/s carry out the various commands of the game in the form of an on-screen persona or "avatar" and in doing so, the immersive stimuli are able to activate the mirror-neurons, which in turn, initiate neuroplastic changes that eventually result in recovery of motor function. Another reason behind the "Nintendo Wii™" being the most popular form of Virtual Rehabilitation technology is the ability of the user to change and adjust the degree of required dexterity and speed of motion according to his/her own requirements.[13]

Various assortment tests such as the Motor Assessment Scale (MAS), Fugl-Meyer (Upper extremity component) Assessment scale (FMA-UE), Wolf Motor Function Test (WMFT), and Action Research Arm Test (ARAT) are reported for the quantification of upper extremity motor function in stroke patients.[13] The ARAT stands out as it is explicitly intended to be time-efficient (an average of 10 minutes being required for administration) and this aspect renders it more desirable than other upper extremity assessment scale alternatives.[14]

Since the efficacy of novel virtual rehabilitative techniques in stroke survivors are still relatively unexplored, the current study intended to carry out a comparison between serum BDNF levels as well as enhancement in upper limb motor function in terms of gross movement, pinch, grip, primary grasp, pre and post intervention in the study and control groups.

METHODOLOGY:

This project was carried out at Holy Family Hospital Rawalpindi in alliance with Islamic International Medical College Rawalpindi after acquiring approval from the Ethics Committees from both establishments. It was a randomized control trial for the duration of one year (from March 2015 to March 2016). 40 stroke patients were selected for this study, who were then randomly designated (by manual balloting) to either the study group or the control group. The inclusion criteria were; first incident of stroke, age between 30 to 60 years, weakened motor capacity of one arm, a time duration of no more than 4 months since the episode of stroke, a basic comprehension of computer/video game commands and radiologically declared stroke by CT-scan or MRI. The exclusion criteria were; other neural disorders, impaired cognizance, dementia or epileptiform disorders, linguistic barriers that would affect the ability to understand the intervention regimen, compromised visual acuity visual, musculoskeletal impediments that could limit movement, and an inability to perform voluntary arm movements.

After acquiring written informed consent, certain baseline demographics and stroke relevant variables of each subject were recorded, including age, sex, blood pressure, affected cerebral hemisphere, type of stroke and handedness. Upper limb "activity capability" was quantified by ARAT, on a scale of 0 to 57. Serum BDNF was measured after taking blood samples.

The intervention for the study group was structured to include CIMT for the upper limb using motion capture video gaming technology (Nintendo Wii™) for four times, 20 minute sessions a week for four weeks (total 16 sessions). The subjects wore a specialized heavy mitt on the uncompromised hand, thereby restricting its use during the intervention. The degree of how challenging each game was, adjusted based on each individual subject's ease of motion and the deftness of the debilitated arm. The target activities of the intervention comprised of a combination of adduction, abduction, extension and flexion of the shoulder joint, wrist joints, pronation and supination of the forearm, finger rolling, pinching, slicing motion, gripping, and arm swinging. The improvement of the subjects on the basis of how the games were played, deftness of command execution and swiftness and agility of movement was recorded throughout the duration of intervention and with each individual's improvement in these parameters, the degree of challenge that the game demanded was increased in a step ladder pattern. The participants were expected to restrict the use of their healthy limb for the majority of waking hours during the day and were asked to keep a track of the number of hours for which they complied with this command on a daily basis.

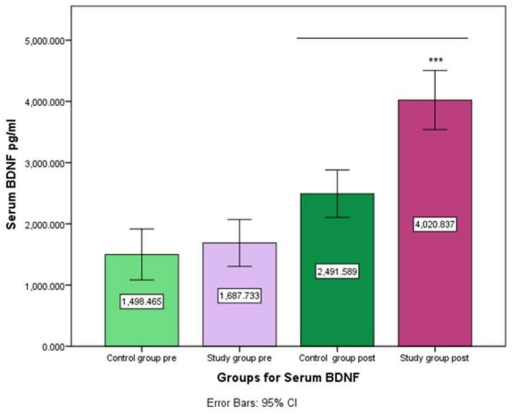
The control group underwent traditional upper limb physiotherapy for 16 sessions (4 sessions for 4 weeks) of 20 minute duration and there was no restriction based on handedness of the training. The control group candidates were made to carry out activities like reaching and pointing, lifting weighted objects with the affected side and various other commands involving the use of both sides of the upper limb like stabilizing a bottle with the healthy hand and attempting to unscrew the cap with the weakened hand and vice versa. Improvements in activity capacity and fluidity of motion were recorded throughout the training period and the skill level demanded by the task commands was increased in a step-ladder pattern accordingly.

Once the period of intervention was over, both the control and study group were evaluated for upper limb motor activity capability (via the ARAT scale) and for serum BDNF, blood samples were drawn. The blood samples taken for serum BDNF level measurement both before and after the intervention phase were first centrifuged to separate the serum and the serum samples were then stored at a temperature of negative 80 degrees Celsius. For quantification of serum BDNF levels, quantitative sandwich ELISA technique was employed. The storage of serum samples and the ELISA procedure was carried out in the multi-disciplinary lab at Islamic International Medical College Rawalpindi. For analyzing the raw numerical data, SPSS 21 software was employed. Results were presented as mean + SD. A p value of < 0.05 was taken as statistically significant. For the comparison of mean serum BDNF results and ARAT total as well as subtest scores between before and after the intervention phase, paired sample t-test was used.

RESULTS:

The difference between the mean post-intervention serum BDNF levels between the study and control group was highly significant (p<0.001) as shown in the figure I. The mean post intervention ARAT scores of study and control group had a statistically significant difference (p<0.001) as seen in table I. All four subtests of ARAT i.e., grasp, grip, pinch and gross movement showed highly significant improvement between the control and study groups.

Figure : Pre- and Post-intervention comparison of the Serum BDNF levels in the control and study groups



***Highly statistically significant between study and control groups p<0.001

DISCUSSION:

Stroke is the leading cause of motor function impairment worldwide, affecting 350,000 individuals each year.[1] Motor function of the stroke survival patients can be recovered up to a varying extent via rehabilitation, depending upon the cause and area of the brain involved. In the current study subjects in both the control and study groups showed marked elevation in serum BDNF levels after the 28 day period of receiving their respective forms of intervention. The difference between the mean serum BDNF values of the control and the study group was highly significant. These changes are supported by numerous studies showing evidence of plasticity driven motor improvement following interventions involving neuro-rehabilitative practices especially those based on exposure to surroundings rich in multimodal stimuli.[15]

Certain studies explored the effect of introducing exogenous BDNF to the ischemic cerebral tissue to look for evidence of functional motor recovery. Ploughman et al in a trial testing the effect of "skilled reaching" in rats found that "BDNF contributes to motor recovery following focal ischemia".[16] It is therefore suggested that the greater the levels of circulating BDNF following an intervention, the greater the effectiveness of said intervention in inducing activity-dependent neuroplastic cerebral reorganization and the greater the subsequent improvement in motor function.

Data regarding circulating BDNF levels has been varied. A trial conducted by Zoladz J.A et al to assess the effect of endurance training on the plasma concentration of BDNF found pre-intervention levels of plasma BDNF to be 10.9+2.3 pg x ml (-1) in young healthy men.[17] Lang et al while studying the "association of BDNF serum concentrations with central serotonergic activity" found Serum BDNF levels of 16.407+7.6 in men and 17.077+7.8 ng/ml in women; a trial comprising 109 healthy individuals (62 men and 47 women).[18] However; It has been shown that BDNF is most active during the "prenatal period" when the development of neuronal circuitry is under its control and then later on in life during the formation of new memories and in processes involving cognition and motor function.[19] Cerebrovascular and neurodegenerative disorders have shown to have a negative impact on the expression of this neurotropin reflected by low circulating levels of BDNF; an event that can be used as a "neurological biomarker" for stroke, Alzheimer's

Table I: Comparison between the mean subtest scores of ARAT pre and post intervention in the study and control groups

Outcome measures	Control group pre-intervention	Study group pre-intervention	p value	Control group Post-intervention	Study group post-intervention	p value
ARAT X (0-57) + S.D	16.80+ 2.707	16.20+3.942	0.578	36.80+ 6.940	48.30+5.768	<0.001***
Grasp X (0-18)	4.90+1.774	4.20+2.567	0.323	10.90+3.401	14.65+2.300	<0.001***
Grip X (0-12)	3.65+0.999	4.05+ 1.395	0.303	7.70+1.218	10.25+1.293	<0.001***
Pinch X (0-18)	6.45+1.932	6.40+1.569	0.929	12.00+2.513	15.40+1.930	<0.001***
Gross movement X (0-9)	1.80+1.735	1.90+2.292	0.877	6.37+1.300	8.00+1.214	<0.001***

disease, Parkinson's disease and cerebral palsy among others. An elevation in serum BDNF in the face of such neuronal disorders could point towards the effectiveness of treatment.[20]

There have been few human studies employing CIMT augmented by Virtual Rehabilitation and even fewer that have used serum BDNF as a barometer for gauging neuroplasticity driven motor recovery in the sub-acute phase of stroke. However, the highly significant increase in the serum BDNF levels in the study group compliments the findings of the animal trial conducted by Livingston-Thomas in which a neuro-rehabilitation regimen clinically similar to CIMT was carried out in Endothelin-1 induced stroke model rats.[21]

Single subject study was carried out by Slijper et al which showed that the motor function strength and agility of the upper limb shows significant improvement after intervention of 5 weeks of video-game centered physiotherapy, assessed by ARAT scores. These findings are in concurrence with the current study's results.[22]

Ample literature showed improvement in specific subtests of ARAT like the one conducted by Christie et al.[23] It focused on showcasing the efficiency of Nintendo Wii as a safe and effective device for neuro-rehabilitative purposes. In this study, the only sub-test of ARAT in which the 9 subjects showed significant ($p = 0.03$) improvement was the "Grip" sub-test.[23] The EVREST trial conducted by Saposnik et al, could be used as a justification for the improved ARAT scores in the current study as it highlighted the direct link between improved upper limb motor capacity and potentiating of not only newly formed synaptic connections in the brain but the salvage of old, reversibly damaged neuronal connection as well, caused by repeated, goal oriented activity, which is the foundation of Virtual rehabilitation.[24]

Indeed, the progress made by the study group candidates of the current study in terms of carrying out fluid and well-coordinated movements by the end of the intervention phase could be attributed to the positive impact of interactive video-gaming on hand-eye coordination, findings which can be corroborated with the trial conducted by Kullman at the Arizona State University which showed marked improvement in the dexterity, grip strength and hand-to-eye-coordination in surgeons who were subjected to Nintendo Wii gameplay.[25]

It is important to note that trials that have used "Wiihabilitation" alone as a means of causing motor function improvement have not contributed on upper limb motor capability improvement as those which have employed a combination of interactive video gaming technologies and standard physiotherapeutic techniques such as CIMT.[26-27] These findings are very encouraging for the current study's result as it too employed a modified physiotherapeutic regimen of CIMT plus Virtual Rehabilitation which proved to be instrumental in bringing about highly significant motor function improvement in its study group participants.

Neuroplastic enhancement led by growth factors such as BDNF seems to respond quite significantly to novel physiotherapeutic approaches such as Virtual rehabilitation if used as an aide with standard techniques such as Constraint Induced Movement Therapy. It is an efficacious and sound method of keeping stroke survivors engaged in and compliant with physiotherapy approaches by inculcating interest and encouraging self-directed therapy time while at the same time bringing about actual, worthwhile motor function improvement; a feat not yet matched by traditional rehabilative techniques . This study does, however, leave room for further exploration, at scale that is much larger, and that which engages a greater demographic of stroke survivors.

CONCLUSION:

Virtual rehabilitation was an efficacious method for Neuroplastic enhancement in stroke patients.

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019088

Contemporary Trends Regarding Knowledge And Practices Of Dental Implants Among Dental Interns Working In Educational Institutes Of Karachi, Pakistan

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ABSTRACT:

Aim: The aim of this study was to assess the information about dental implants among dental interns and to relate their perception of future dental implant practice.

Study Design and Setting: A cross-sectional study was conducted on dental interns of various dental teaching colleges of Karachi including public and private institutions.

Methodology: The instrument used was a self-administered, structured, closed-ended questionnaire which was modified measuring tool for the dental interns' knowledge and perception towards implant dentistry. The data collected from the study was analyzed using SPSS.

Results: Two hundred and seventy dental interns of 5 different colleges of Karachi filled a questionnaire about the knowledge and future perception of dental implant practice in general dentistry. It was observed that majority of the dental interns 44.2% did not have adequate knowledge of dental implant and 87.6% encourage to improving the undergraduate syllabus of dental implants.

Conclusion: This study showed limited knowledge and awareness about dental implants among dental interns, but they highly encouraged in improving the curriculum of dental implants at undergraduate level.

Key Words: Dental implants, Dental Interns, Implant Dentistry.

INTRODUCTION:

Implant dentistry is one of a kind in having the capacity to accomplish the dental objectives.[1] The replacement of dental implants in the restoration of mostly partially and complete edentulous jaws have turned into an entrenched and accepted contemporary clinical strategy because of its predictability.[2] Dental practice has encountered astounding change in dental materials of restoration, management and planning of cases that are typically viable for the better prognosis of tooth misfortune.[3] Scientifically driven methodologies have been developed that give the patients' esthetically and functionally great alternatives for teeth replacement.[4] The partially edentulous patient is would now able to experience substitution of a single tooth or a few missing teeth with implant retained crowns that give a similar feel they had with their natural teeth.[5] Using implant retained removable prostheses in complete edentulous patient increase the confidence than that conventional complete denture wearers normally experience.[6] In a study, it was found that self-confidence increased in 88% of patients after implant treatment and 98% stated that their oral health had improved[7]. This success and satisfaction of dental implants[8] in turn results in a widespread use of dental implants within the dental professional community[9]. The restoration of dental implants is thought to be as a specialist technique for oral health care that was practiced by implantologists only and required preparation beyond the regular dental school educational programs.[10] However, despite the fact that implant dentistry has separated field of specialty, it remains a complex subject requiring a sound establishment to gain competence in this field.[11] Literature review, recommended that most patients seek their dental specialists to give them information and treatment in regard to dental implants.[12] These undergraduates are presented to the theoretical information behind the act of dental implant just as a possibility for tooth substitution so they can advise patients of their treatment options.[13] However, implant practice should be included in undergraduate program to acquaint the essential practice with maturing general dentist. Awareness amongst the undergraduate medical/dental students concerning any new update in their field will be beneficial in educating the

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Received: 02-08-2019
Accepted: 25-11-2019

general population. Undergraduate students are considered the ambassadors of the specialty.[14]A baseline data related to the prosthodontics practices among practicing dentists in any population is critically important. From knowledge through indexed literature there are no studies that report the trends in prosthodontic practices among GDPs in a Pakistani population. Such data is vital for understanding the current patterns in practice of GDP and for planning of widespread oral health care for the population[15]

The aim was to assess the knowledge of dental implants among dental house officers and to relate their perception of future practice of implants.

METHODOLOGY:

A cross-sectional study was conducted on dental interns of various colleges of Karachi including public and private institutions. Ethical clearance was obtained from the Ethics Committee of Baqai Medical University. Approximately 900 dental interns are recruited every year in 14 dental colleges of Karachi. The sample size was calculated by sample size formula n = [DEFF*Np(1-p)]/ [($d^2/Z^2_{1-á/2}$*(N-1)+p*(1-p)] at 95% confidence interval, where, Z á / 2 = 1.96, p= 50% sample proportion and d = 5% of precision error was takenand sample size obtained was 270. According to sample size of five dental colleges; 3 colleges from private pool and 2 from public dental colleges' pool were chosen. Written consent was obtained from study participants after explaining in detail about the study. The instrument used was a self administered, structured, closed ended questionnaire which was modified for the dental interns' perception, and knowledge towards implant dentistry. The content validity for the questionnaire was analyzed as per the procedures given by Lawshe[16]. Content validity of the questionnaire was measured by taking the opinion of 5 subject experts, and the questionnaire was modified accordingly. If any question had a content validity ratio of <0.99, the question was deemed as inadequate and was deleted or changed after consultation with the experts. After the validity assessment, out of 12 original questions, 5 were retained without any change, 3 were modified, and 4 were deleted. The modified questionnaire consisted of 8 items. Part A comprised of four questions related to the knowledge of dental interns toward implantology. Part B comprised of 4 questions related to perception of dental implant practice. All the interns of the 2018–2019 batch were briefed about the study. Only those interns or house officers were included who had done the rotation of restorative dentistry departments. Those who consented filled up the questionnaire of about 10 minutes. Descriptive analysis was performed by calculating the frequencies and percentages. The analysis was performed using the Statistical Package for the Social Sciences version 20.

RESULT:

Total of 275 participated in the study, out of which 67 were gathered from Dow Dental College, 72 were from Karachi Medical & Dental College, 53 were Liaquat Medical & Dental College, 34 from Ziauddin University and 49 from Baqai Medical University. Out of which 44.2% had moderate knowledge of dental implants, 46% choose implants as choice of replacement because of long lasting treatment option, and most of the participants that is 64.6% thought case selection is the prime factor of better prognostic results. While 43.3% thought its frequency as treatment option could be hinder by its cost. In response to attitude, half of the participants 51.8% agreed that implant dentistry was the part of the BDS curriculum but about 87.6% thought to expand the syllabus of applied dental implant. Most participants 70.4% preferred to train in tailored implant course during their house job period to improve their practice of dental implant and 53.5% also liked to learn from the certificate course during their house job. 87.7% did not experience any dental implant patients in their training period.

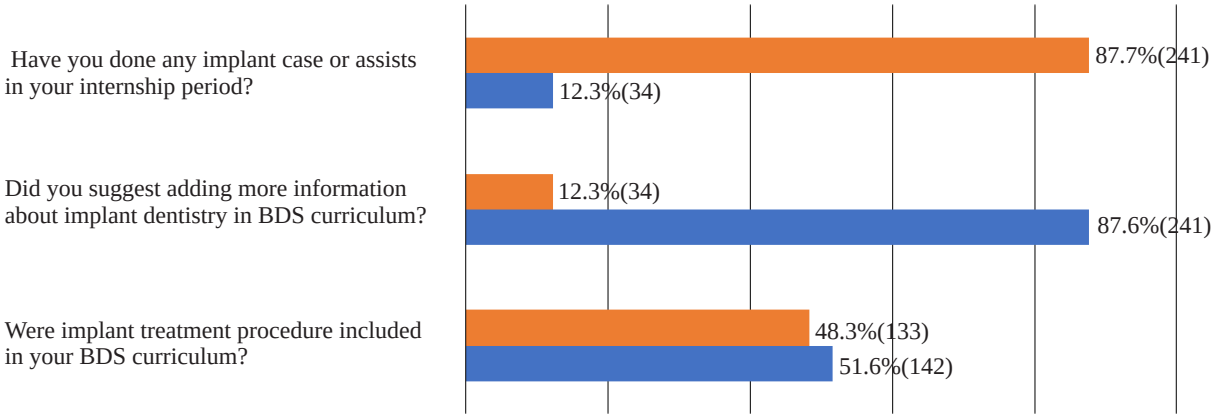
DISCUSSION:

This study was carried in four different dental college hospitals where internees were posted for their clinical rotation. This study assesses the knowledge and perception of interns towards implants and their perception to use it in future practice. They all studied local council approved curriculum, which includes the basic information of implant dentistry in restorative subjects of undergraduate course. Implant has been the frontline of dental practice over the past decades.[17] With spread of awareness and success rate of implants, patients prefer it as the best treatment option. In our study, participants were not confident enough about their basic dental implant knowledge. Implant treatment is a chosen procedure by patient in most treatment cases[18]so complete information on implant and alternative treatment options must be explained to the patient so that they can make an educated decision.[19]A study on the Austrian population found that dentists are the primary source of patient information on dental implants followed by friends and acquaintances, print media, and general dentist.[20] Health workers are an integral part of the health profession and therefore, the poor knowledge of dental implant (9.7%) recorded among them in this study could be as a result of lack of practice of dental implantology by dentists in their hospitals.[21] Other study showed an average, 80 out of 110 General dental practitioners had basic knowledge about implant dentistry and 65.5% were not aware about advance surgical procedures like sinus lift, guided bone regeneration etc., for dental implant surgery.[22] Only 9 (6.3%) interns perceived that they were well prepared in replacing the teeth with implants.[23] In an other study, 39.11% of the dental interns were very confident regarding the knowledge of implant procedures. The interns were little confident regarding the additional surgical procedure (23%), elevating the flap (13%), and suturing of gums (28%) in implant procedure.[24]

Table 1: Veriable regarding knowledge of dental implant

	Responses
How do you evaluate your knowledge regarding dental implant?	
a) Adequate	81(29.3%)
b) Moderate	122(44.2%)
c) Insufficient	73(26.4%)
Why do you prefer dental implant as replacement choice of treatment?	
a) Aesthetics	22 (8%)
b) Conservative (does not required reduction of abutment teeth)	120 (43.6%)
c) Long lasting	127 (46.1%)
d) Don't know	6 (2.1%)
What is the most important factor for successful prognosis of implant treatment?	
a) Selection of case	178 (64.7%)
b) Type and materials of implant	5 (1.8%)
c) Compliance of patients	27 (9.8%)
d) Surgical technique	32 (11.6%)
e) Operator's personal experience	26 (9.45%)
f) Don't know	7 (2.5%)
Which of the following reason affect the popularity of dental implant?	
a) Expensive	119 (43.2%)
b) Invasive procedure	86 (31.2%)
c) Lack of awareness	70 (25.5%)
From which course might you want to get training on dental implant?	
a) Continuing dental education of 2-3 days' workshop	43 (15.6%)
b) Extensive certificate courses of months or one year	147 (53.4%)
c) Fellowship programs	23 (8.3%)
d) MSc programs	62 (22.5%)

Graph I: Questions on perception of future practice of dental implant



The awareness found was less in this study as compared to above mentioned studies which may be because of low level of education and the study was conducted in teaching hospital where most of the patients were from rural community.[25] However, in our study 46.1% said they will choose implant because it retained longer than other options. The study of another population about advantages of dental implants, 55.4% reported that the main advantage of dental implants is its conservational dental approach as compared to other fixed prosthesis (FPD).[26] Upon asking about the reason of rejection by patient to having implant procedure about 43.2% suggested that cost can highly affect the decision of patients followed by fear of invasive procedure. The other study was conducted regarding public awareness and knowledge of implant revealed that cost was the biggest barrier of implant treatment.[6] Furthermore in India, dental students were asked about having dental procedure and discovered that 17.2% of students were refused to have procedure on themselves

and 31% of students were confused to having procedure as they were not aware about it.[27] When asked whethe the course of applied implantology was the part of BDS curriculum, 48.3% were not even sure and 87.6% suggested to expand the course of dental implantology in the BDS curriculum**.** According to Saudi study 50% of dental students expressed the need of further knowledge on dental implants and 40% agreed that they did not have enough information regarding the subject**.**[28] Another study was undertaken to assess the knowledge of dentists preferring implants as a choice for replacement of missing tooth/teeth, it can be suggested that with the emerging priority of implants in general practice, there is a need to introduce dental implants into dental curriculum.[24]In this study; regarding acquiring knowledge in the field of implant dentistry 53.4% choose certificate program, similarly in Barcelona 71% preferred one-year certificate or modular courses by dental implantologist.[29] Other study in India showed over 70% of subjects feel the need to have implant training as a part of their undergraduate clinical curriculum whereas about 56.6% feel that it should be made into a separate specialty.[30] In an other Indian study; whopping response of 91.7% students was revealed as they wanted more information to be added in their BDS course because this will directly affect how well they learn and use implant treatment options in their future dental practice.[31] However, in this study 87.7% students diet not have practical experience of dental implant. An, Iraqi study showed positive response regarding observation and assistantship of 5th year students with 55% in surgical placement of the implant and 73% students had their practical experience in their college.[32] Whereas, a study in Nepal showed 90.9% general dental practitioners were not practicing dental implant in their routine practice due to lack of knowledge and confidence.[13] In Enugu Nigeria, 7.2% dental interns preferred dental implants as a choice of treatment.[21] In North Karnataka India, dental practitioner were asked about dental implant cases in their practice in which 80% GDP did not practice dental implants, while others referred the cases to specialists.[33] The future perception of implants is appreciable, but there is need of strengthening education in young dentists to reinforce knowledge and awareness of dental implants in education sectors. The limitations of this study were sample size and limited use of implant supported prosthesis in dental teaching hospitals as compared to private clinics. Currently, there is no hands-on patient based or mannequin-based teaching of dental implants for undergraduates. These students are exposed to the general theory behind the use of dental implants only as an option for tooth replacement so that they are able to inform patients of their treatment options. Hence, within the limitations of our study, we propose that the B.D.S. curriculum be modified appropriately to expose students to dental implants from the diagnostic, treatment planning, surgical, and restorative perspectives.

CONCLUSION:

This study found that the majority of the dental interns' confidence of future practice about dental implants was constrained due to clinical source of information which has not been attained. Our study found that 87.6% of dental interns wanted more information to be provided regarding dental implants in their B.D.S. program.

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019107

Effect of Priming Principle on Propofol Dose Required to Induce General Anesthesia

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ABSTRACT*:*

Objective: To compare the mean induction dose of Propofol to induce general anesthesia by conventional method versus mean induction dose after applying priming principle.

Study Design and Setting: Randomized controlled trial at Operation theatre complex, Shalamar Hospital, Lahore from November 2016 to May 2017.

Methods: A total of 100 patients aged 18-55 years were equally divided into control and study groups. After standard anesthetic monitoring, intravenous propofol was used for induction of general anesthesia by conventional method in Control (C) group and by applying Priming principle in Study (S) group. Total dose requirement of propofol was noted. Data was analyzed in SPSS version 20 and paired sample t-test was applied. P-value of < 0.05 was considered as significant.

Results: The mean induction dose of propofol was 70.90 ± 16.77 mg in study group (S) as compared to 94.60 ± 20.22 mg in the control group (C). The difference of mean induction dose in both groups was 23.7± 3.45 mg and thus p-value of 0.000.

Conclusion: There was significant reduction of dose of propofol required to induce general anesthesia in elective surgical patient by applying priming principle.

Keywords: General anesthesia, Priming principle, Propofol.

INTRODUCTION*:*

We are living in the era of day care surgery and anesthesia. Unusual and prolong hospital stay due to anesthetic drugs definitely increases economic burden and risk of hospital acquired complications. Propofol is the most commonly used intravenous anesthetic induction agent used due to its property of smooth and more rapid induction, rapid awakening, clear headed recovery, decreased incidence of post-operative nausea and vomiting, better intubating conditions and upper airway integrity compared to thiopentone.[1,2] However, the single bolus induction dose of Propofol causes profound hemodynamic instability due to direct myocardial depressant and decreased systemic vascular resistance.[2,3]

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Received: 03-10-2019
Accepted:12-12-2019

Muhammad and colleagues found that single bolus dose of 2mg/kg resulted in the decrease of 26-28% of systolic blood pressure, 19% of diastolic blood pressure and 11% of mean arterial pressures.[4] The literature review reveals that various techniques can be used to reduce the induction dose requirements of propofol i.e. concurrent use of nitrous oxide, opioids, barbiturates like thiopentone, benzodiazepines like midazolam, augmentation with local anesthetics or magnesium sulfate and use of "Priming Principle".[8,9] Priming Principle has been successfully used to reduce the conventional dose of non-depolarizing muscle relaxants for early achievement of intubating condition.[8,13,14]

Priming principle has been successfully practiced to reduce the total induction dose of Propofol in different studies. Sanket et al used Midazolam and Fentanyl with propofol as priming agents in their study. They found a statistically significant ($p<0.05$) 27.69 % reduction in induction dose requirement in study group after applying Priming principle.[1] Number of techniques have been tried to counteract the hypotensive effects of propofol i.e. slow administration of drug, preloading, and administration of vasoactive agent (phenylephrine) to raise blood pressure.[4,13] However; Priming principle has not been studied on induction dose of propofol among local population in Pakistan and indeed it was the rationale of the study.This study was designed to determine the effects of priming principle on total dose requirement of propofol for induction of general anesthesia to reduce the dose of propofol. Therefore this study was aimed to compare

the mean induction dose of Propofol to induce general anesthesia by conventional method versus mean induction dose after applying priming principle.

METHODOLOGY*:*

This randomized control trial was conducted at operation theatre complex, Shalamar Hospital, Lahore form November 2016 to May 2017.Non-probability consecutive sampling technique was used to calculate the sample size of 100 patients with 95% confidence level and 80% power of test.

Following approval from our IRC; 100 patients of age 18-55 years with American Society of Anesthesiologists (ASA) physical status I & II were included. These patients were scheduled for elective surgery under general anesthesia i.e. cholecystectomy, umbilical hernia repair, incision and drainage, thyroidectomy, EUA (examination under anesthesia), arthroscopy, corrected surgery for upper limb fractures, tonsillectomy & septoplasty. Patients refusing the consent to participate, patients with history of allergy to opioid and egg, anticipated difficult airway (Mallampati class III & IV), pregnant and lactating mothers were excluded from the study. Informed consent was taken from each patient, ensuring confidentiality and no risk involved to the participants. Patients were equally divided into control (C) and study (S) groups by lottery method. After transferring the patient to the operation theatre, intravenous line was secured and standard anesthetic monitoring was attached. Propofol and plain Lidocaine were mixed to decrease the chances of pain on injection.[5] Midazolam 0.03 mg/kg and nalbuphine 0.1 mg/kg were given intravenously over 30 seconds. This was followed by administration of propofol by conventional single bolus dose of 2 mg/kg in Control (C) group. Priming Principle was used in study (S) group; 20 % of the calculated dose of 2 mg/kg was administered initially and remaining propofol was given after 30 seconds till the loss of eyelash reflex. Total dose requirement of Propofol until the loss of eyelash reflex was noted. This was followed by muscle relaxant to facilitate the tracheal intubation.

INDUCTION DOSES OF PROPOFOL*:* **Conventional method:** Conventional single bolus dose of propofol (2mg/kg) was given for the induction of anaesthesia.

Priming principle: Initially, 20% of calculated Propofol dose (2mg/kg) was given as priming agent followed by 30 seconds interval. Remaining propofol was administered till the loss of eyelash reflex.

Data was entered and analyzed by SPSS version 20 p-value <0.05 was considered statistically significant. Quantitative variables such as age, weight BMI and required dose of propofol in both groups were presented as mean and standard deviation. Gender and ASA physical status was presented as frequency and percentages. The independent sample t-test was used to compare the outcome variables i.e. mean induction dose of Propofol.

RESULTS*:*

Among Control Group (C): The mean age was 36.46 ± 11.59 years with range of 18 years to 55 years. Out of 50 patients, 20 (40%) were male and 30 (60%) were female. Mean weight was 66.74±15.11 kg and BMI was 28.42±4.99 kg/m^2. 38 patients (76%) were ASA I and (24%) were ASA II. Mean induction dose of propofol was 94.60-±20.22 mg. (Table I)

Study Group (S): Mean age was 33.88 ± 11.05 years with range of 18 years to 54 years. Out of total 50 patients, 23 (46%) were male and 27 (54%) were female. Mean weight was 68.28±14.42 kg and BMI was 28.22 ± 5.15 kg/m^2. 39 (78%) patients were ASA I and (22%) were ASA II. Mean induction dose of propofol was 70.90±16.77 mg. (Table II)

Using unpaired t-test, the difference of mean induction dose in both groups was 23.7± 3.45 mg & p-value 0.000 showed statistically significant results (Table III).

Table I: Mean induction dose of propofol (mg) by conventional method:

Mean induction dose of Propofol (mg)	Number of patients	50
	Minimum dose	60
	Maximum dose	150
	Mean	94.60
	Std. Deviation	20.224

Table II: Mean induction dose of propofol (mg) after applying priming principle

Mean induction dose of Propofol (mg)	Number of patients	50
	Minimum	21
	Maximum	39
	Mean	70.90
	Std. Deviation	16.772

Table III: Unpaired t-test for Dose of propofol:

	Group	Number of patients	Mean	Standard Deviation	Standard Errorof Mean	P-Value
Dose (mg)	Control	50	70.90	16.772	2.372	0.000
	Study	50	94.60	20.224	2.860	

DISCUSSION*:*

Anesthesia induction is the most important and eventful phase during the entire course of general anesthesia. Propofol, a phenol derivative is commonly used for induction of anaesthesia and procedural sedative agent for emergent procedures.[9] Due to its rapid onset, short duration of action and suppression of airway reflexes, propofol has acquired the most preferred choice for induction of anaesthesia.[10] However, the hemodynamic instability and pain on injection caused by the conventional induction dose of 2–3 mg/kg is the major concern for the anesthesiologist. [6,10,20]

Multiple strategies and methods have been adopted in an effort to reduce the induction dose requirements of propofol. [9,13] The technique of priming principle involves the use of smaller doses of the priming agent before the use of single bolus dose. The application of this priming technique to the use of propofol either as an induction agent or as an infusion for ICU sedation has distinct advantages.[16, 17] There is a decrease in total dose of propofol required for induction as well as pain on injection appears to diminish considerably [18]. The hemodynamic changes are also less pronounced. [20]

In the present study we have tried to evaluate whether priming principle applied to the induction dose of propofol reduces the total dose requirement in our population.

The mean induction dose required in the priming group was significantly lower 70.90 ± 16.77 mg than in the control group 94.60 ± 20.22 mg. There was a significant difference 23.7± 3.45 mg of mean induction dose of propofol in both groups.

Our study results were different from a previous study[1] in which mean induction dose of propofol in control group (C) was 94.60 ± 20.22 mg as compared to 113.27 ± 18.68 mg while 70.90 ± 16.77 mg as compared to 81.37 ± 15.82 mg in study group (S). The reduction of propofol dose in our study was 27 % as compared to 25 % in other study.

Thus, we found that propofol priming principle technique attains comparable anesthetic depth of anesthesia with a significantly lower dose when compared to the conventional, single bolus dose of propofol during induction.

However, few limitations of the study included; single center trial only covering ASA I & II, non-pregnant and elective patients. The use of an invasive arterial blood pressure monitoring could have revealed more specific results.

There is room for large multicenter trials and different population of patients to determine the important role of this priming principle. Further avenues of research include use of propofol priming technique impacting the pain on injection and incidence of postoperative nausea & vomiting.

CONCLUSION:

The induction dose requirement of propofol is significantly lower in the priming principle group when compared to the conventional induction group in elective surgical patients

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019098

Anatomical Variations of Frontal Sinuses Among The Male and Female Genders Living in Karachi

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ABSTRACT

Objective: To determine morphology and variation in dimensions of frontal air sinuses in male and female genders living in Karachi.

Study Design and Setting: It was a cross sectional study and was conducted at Radiology Department, JPMC.

Methodology: The total number of study participants were 216. The research subjects were divided into two equal groups of males and females each having 108 members. The mean age of the participants was calculated to be 35.14 ± 8.68 years. The study subjects were recruited from Radiology Department, JPMC, Karachi. After taking written informed consent, Water's (occipito-mental) view radiography was done to measure the parameters of height, width and area of the frontal air sinuses. The included variables were the demographic data and the physical examination to exclude facial anomalies. All the measurements were recorded and the measurements were saved by the help of Radiant DICOM digital software.

Results: The parameters of height, width and the area of frontal sinuses showed highly significant variability on both the right and the left sides. All the dimensions were highly significantly greater in the males as compared to the female study participants (p=0.000). The Independent-Samples T Test was applied to compare the two gender groups.

Conclusion: The parameters of height, width and area of frontal sinuses were greater in the males as compared to the females on both the left and the right sides.

Key words: Anthropology, Frontal sinus, Sexual dimorphism

INTRODUCTION:

The humans living in a society have their specific identities. The living individuals are named and they are known to the others by their personal appearances. As the identity of the living is important similarly it is equally vital and essential to know about the identification of the deceased. The deceased need to be identified where there are catastrophes like typhoons, earthquakes, bomb blasts, tsunamis etc. Other major utility is for the medicolegal cases, for social reasons and in cases where financial decision have to be taken.[1]

When dead bodies are in intact shape and organization, they are identified on basis of structural anatomy of face. At instances when the bodies are severely damaged and disguised several methods have to be adopted for the purpose of identification. It has been reported that over a period of last ten years the disaster rate and the causalities related to those incidents have increased. This has created enormous load on forensic science experts as well as anthropologists. The advancement of the forensic science has made possible for the anthropologists to recognize the unknown individuals with great confidence.[2] A report on the terrorists activities in Pakistan has mentioned increase in the incidence of such activities from the period of 2011 to 2015.[3]

The technology involved in forensic anthropology uses the knowledge of the subject of anatomy to ascertain the characteristics and uniqueness of the human body. The investigation requires keen examination of the body's structural organization and details at the spot of the tragic incident. Several years of the researches and experimentations have led to the evolvement of several procedures of human identification. The scientific methods are extremely helpful in situations when the identity becomes a challenge. Soft tissue prints imaging and DNA analysis of the body remains are one of the available methods used by the forensic anthropologists to solve their complex tasks of knowing unidentified bodies.[4,5] In cases where soft tissue is lost due to the extremes of temperatures or decomposition, anthropological studies depend on the bony structures that are stronger enough to remain intact after fatal disasters. The simple yet cost effective technique of radiology can serve as an effective tool in the process of identification of the victims.[6] The radiological methods are far cheaper as compared to the other methods of personal identification. Forensic radiology has become an integral component of the forensic science because of its simpler methodology and cost effectiveness.[7]

Among the anthropological identification tools, skulls are helpful in identification. Skull is a part of human body that

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Received: 17-09-2019
Accepted: 06-12-2019

is made of strong connective tissue. It is the second last part to persist after teeth when a person dies.[8] The parts of the skull have characteristic features which make them one of the valuable sources in cases where the body's soft tissues are lost and it is in decomposed state.[9] The parts of the skull used for human identification include the nasal septum, mastoid process, sella turcica, teeth and para nasal sinuses.[10] The superimposition techniques involving the structures of the human skulls have helped in identification of the deceased.[7]

The anatomy of the paranasal sinuses can help the forensic anthropologists in human identification due to the peculiar characteristics which are unique to all the human beings.[10] The stronger bony identification tools can be identified by a simple and less expensive method called radiography. The methodology of radiography aids in determining the identification of persons that are otherwise in decomposed or putrefied state.[11]

The frontal sinuses anatomy has proven to be useful due to their unique features.[12] Over the years with the advancements of the techniques and increased research work, usefulness of frontal sinuses anatomy in personal identification cannot be overlooked. Reasearch based on matching and comparison of the frontal sinuses, mentioned the similarity of anatomical structures in terms of the antemortem and the postmortem findings.[13,14]

The terrorists' activities as well as natural disasters are on the rise in Pakistan. According to the Emergency Database (EM-DAT) and Global Terrorism Database (GTD) report, from the period of 2003 till 2017, the number of terrorists activities were 289 in number while the natural disasters were recorded to be 45.[15] Various researches have been conducted on frontal air sinuses across the world.In Pakistan literature search shows that till now no research paper has been published that was related to the anatomical variation and its significance in the field of anthropology. Since variations are present among the people living across the world, it's important to conduct a study among the males and females of Pakistan and indeed it was the rationale of the study.

METHODOLOGY:

The study was conducted at the Radiology Department, JPMC. Before commencing the research ethical approval was obtained from the Ethical Review Committee of Bahria University Medical and Dental College and the Institutional Review Board of Jinnah Post graduate Medical Center. The sample size was calculated by the help of open epi version 3 calculator and it was found to be 214. The total number of the study subjects included in the present study was 216. The total duration of the study was 6 months and individual study period was 40 minutes for each participant. The research participants were divided into two equal groups of males and females. Each gender sub group consisted of 108 members. The mean age of the participants was calculated to be 35.14 + 8.68 years.

The study subjects were recruited from the Radiology Department of Jinnah Postgraduate Medical Center, Karachi. Males and females free of paranasal diseases within age range of 20 to 50 years were included in the research. Participants who gave past history of paranasal sinus diseases or who had surgeries of paranasal sinuses and pregnant ladies were excluded from the research. Written informed consent was obtained before the study. The included variables were the demographic data and the physical examination to exclude facial anomalies. The present study included the research subjects above 20 years in order to include individuals with full frontal sinus development. The participants were physically examined before they were selected for radiography. The view used for radiography was Water's (occipito-mental) view. The radiographic procedure for the frontal sinus imaging was carried out in the room number 2 of the radiology department. The participants were asked to stand erect with chin raised. The distance was 36 cm from source to film.The X-ray beam was at right angle to the receptor and 45 degrees to the orbito-meatal line. The X-ray beam was inclined 1 inch above the level of external auditory meatus. The study parameters were height, width and area of the right and left frontal air sinuses. The parameters were saved in the JPEG format and then the measurements were carried out by the help of Radiant DICOM digital software.

The measurements were performed according to the Ribeiro's criteria.[16] Base line A was drawn on the upper limit of both the orbits. The highest point of the right frontal sinus was marked as B. A perpendicular line C was drawn from the highest point of right frontal sinus to the base line A. The perpendicular line C was considered as the height of the right frontal sinus. The highest point of the left frontal sinus was marked as D. A perpendicular line E was drawn from the highest point of left frontal sinus to the base line A. The perpendicular line E was considered as the height of the left frontal sinus. Line passing at the most lateral point of right frontal sinus was marked as F. A perpendicular line G represents maximum distance drawn from the most lateral point of right frontal sinus to the midline septum. The perpendicular line G was considered as the width of the right frontal sinus. Line passing at the most lateral point of right frontal sinus was marked as H. A perpendicular line I represents maximum distance drawn from the most lateral point of left frontal sinus to the midline septum. The perpendicular line I was considered as the width of the left frontal sinus. Right area of the frontal air sinus was calculated as a product of right height and right width. Left area of the frontal sinus was calculated as a product of left height and left width.

SPSS version 23.0 was used for analysis of the data. The Independent T Test was used to compare the gender groups.

The continuous data was reported as mean ± SD. The results were regarded as significant when the p value was < 0.05. The result were regarded as highly significant when the p value was < 0.001.

RESULTS:

The total study participants were 216 in number. They were divided into two equal groups of male and female genders with 108 participants in each sub group. When mean heights of the right and left frontal sinuses were compared between the male and female gender groups, highly significant variations were noted for both the right and left frontal air sinuses. Statistically, males have significantly higher height than females on both the right and the left sides (Table 1).

When mean widths of the right and left frontal sinuses were compared between the male and female gender groups, highly significant variations were noted for both the right and left frontal air sinuses. Statistically, males have significantly higher width than females on both the sides (Table 2).

Table 1: Gender wise comparison of mean heights of right and left frontal sinuses

Parameter	Gender	Mean ± SD	P value
RT Height (cm)	Male	2.30 ± 0.70	0.000**
	Female	1.97 ± 0.62	
LT Height (cm)	Male	2.63 ± 0.66	0.000**
	Female	2.30 ± 0.63	

RT Height: Right frontal sinus height
LT Height: Left frontal sinus height
Test applied: Independent Samples T Test

Table 2: Gender wise comparison of mean widths of right and left frontal sinuses

Parameter	Gender	Mean ± SD	P value
RT Width (cm)	Male	2.72 ± 0.65	0.000**
	Female	2.41 ± 0.60	
LT Width (cm)	Male	3.53 ± 0.65	0.000**
	Female	3.21 ± 0.61	

RT Width: Right frontal sinus width
LT Width: Left frontal sinus width
Test applied: Independent Samples T Test

Table 3: Gender wise comparison of mean areas of right and left frontal sinuses

Parameter	Gender	Mean ± SD	P value
RT Area (cm)	Male	6.58 ± 2.89	0.000**
	Female	5.05 ± 2.30	
LT Area (cm)	Male	9.66 ± 3.60	0.000**
	Female	7.70 ± 3.01	

RT Area: Right frontal sinus area
LT Area: Left frontal sinus area
Test applied: Independent Samples T Test

When mean areas of the right and left frontal sinuses were compared between the male and female gender groups, highly significant variations were noted for both the right and left frontal air sinuses. Statistically, males have significantly higher area than females on both the sides (Table 3).

DISCUSSION:

The identification of the victim is a difficult task when mass destructions and explosions occur. The identity can be established by several methods depending on the status of the dead body. In cases when there are soft tissues available, finger printing and DNA analysis can be done. On the contrary, when there are skeletonized bodies, the available option remains the identification of the deceased through unique features of the bones. Antemortem comparison of the deceased structures with that of the postmortem remain the cornerstone of identification. DNA analysis is possible by the help of polymerase chain reaction. The extreme heat as present in blasts and mass explosions can interfere with the quality of sample available for DNA analysis.[4,5] In cases of skeletonized bodies, frontal sinus anatomical details examination by radiography is a simple yet authentic method for identification.

Frontal sinuses have unique configuration in every individual. The variation in the anatomical configuration of the frontal air sinuses was observed in a research on the Mexican adults. No two frontal sinuses have the same measurements and therefore they are considered to be one of the best tools in identification of the unknown dead bodies.[17] The present study has also documented variability and unique features between the male and female genders.

The present study included the study subjects in between the age groups of twenty to fifty years. Similar age range was considered as an inclusion criteria in a study on Iranian adults.[18] It has been observed that the developmental period of the frontal air sinuses is completed by the age of fourteen years.[19] According to the published researches, the development of the frontal air sinuses is completed by the age of twenty years.[20,21] The present study included the research subjects above 20 years in order to include individuals with full frontal sinus development. A research article has documented that age related changes occur in the frontal air sinuses after the age of 60.[22] This is the reason to keep the maximum age limit to 50 years so that normal anatomical morphology can be observed.

The dimensions of the frontal air sinuses in the present study were found to be different when males were compared with the females. The parameters were observed to be greater in dimensions for the males as compared to the females who participated in the present research. A research article published in the Journal of Forensic Radiology and Imaging mentioned about a study that was conducted on the Egyptian population. It was documented that significant difference

in the dimensions between the males and the females were also observed.[23]

In our study, the mean heights of the right frontal air sinuses were found to be greater in the males as compared to the females study participants. Variations in terms of mean heights were also recorded when left frontal sinuses were compared between the two genders. Similar results were shown by the researches conducted in India in which the dimension of the right and left frontal sinuses heights in males were bigger as compared to that of the females in the study and the results were statistically significant both on the right and the left sides.[17] Previous studies on the adults of Nigeria also showed parallel findings with documented greater dimensions for the males as compared to the females. The results were found to be significant on the left sides and they were non-significant on the right side.[24]These variations in height observed in the present study can be attributed to the differences in the general structural anatomy and the growth between the two genders.[25]

The current study has showed that the mean widths in males are bigger in dimension in the males in comparison to the females both for the right and left frontal sinuses. The present study's result are in concordance with a morphometric study done on the adult individuals of Karnataka. The mean widths of males were bigger in dimension as compared to the females but the results were statistically significant only on the left side and the right frontal sinuses mean width documented non-significant differences.[26] Comparable findings were observed in between the males and the females of Kashmir with significant results both for the right and left frontal sinuses mean widths.[27] Craniofacial architecture contributes in determining the size of the frontal sinuses. The size of the bones differ between the two genders. Greater the size of the frontal bone, greater will be the size of the frontal sinus. The facial architecture is larger in the males than the females.[28] This could be the explanation of wider widths of frontal air sinuses in the males in contrast to the size of widths in the females.

In the present study, the mean area of the left frontal sinus in the males was measured to be bigger in dimension in the males when the data was evaluated against the females. Analogous findings were observed in the researches conducted on individuals of Turkey with significant results both on the right and the left sides of the frontal air sinuses.[29] A research conducted in Moradabad, India documented contrary findings to the findings of the present study. The mean area reported for the females on both the right and the left sides of frontal air sinuses documented comparatively bigger dimensions for the females as compared to the male study participants but the results were not statistically significant.[30] The smaller areas in females compared to the males may be due to the overall anatomical variability between the two genders.

CONCLUSION:

The parameters of the height, width and area of frontal sinuses were greater in the males as compared to the females on both the left and the right sides in the males and females living in Karachi.

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019124

Protective Effects Of Tecomella Undulata Stem Bark Extract On Isoniazid Induced Hepatotoxicity: Based On Liver Enzymes And Histopathology In Rat Model

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ABSTRACT:

Objective: To evaluate the hepatoprotective effects of Tecomellaundulata stem bark extract on isoniazid induced hepatic damage based on liver enzymes and Liver function test in rat models.

Study design and Setting: An experimental study conducted at Department of Pharmacology at Al-Tibri Medical College and Hospital, Isra University Karachi Campus and Dow University of Health Sciences, Karachi.

Methodology: Total twenty-four rats were studied. The albino rats that were male, healthy, and weighing 200-250grams were included in this study. Rats were divided into four groups, each group having six rats and treated once daily orally for 30 days. Group A was control group and treated with normal animal diet and water; Group B was Isoniazid treated group and induced by oral administration of Isoniazid (INH) 50mg/kg. Group C was treated with Isoniazid 50mg/kg and Tecomellaundulata bark extract with low dose of 200mg/kg . Group D was treated with Isoniazid 50mg/kg and Tecomellaundulata bark extract with high dose of 400mg/kg . All the animals were weighed before commencement of the study. Liver enzymes were noted after the end of experiment. P value of <0.05 was taken as significant.

Results: While comparing the mean values of AST,ALT, ALP and GGT in all four groups group; the statistical significant difference (p<0.001) was found. The mean levels in of total Bilirubin in group A was 0.69 ±0.01, group B 1.04 ±0.04, in group C was 1.15 ±0.39, and in group D was 1.04 ±0.44 with the significant difference (p=0.004).

Conclusion: Tecomellaundulata has a protective effect on isoniazid induced toxicity on liver as evidenced by liver function test on rat models.

Keywords: Isoniazid induced hepatotoxicity, Liver enzymes, Tecomellaundulata

INTRODUCTION:

The plants are used as medicine due to low cost and natural source of remedy. According to WHO, 80% of developing countries are using medicinal plants for the sake of treatment.[1-3] It is a well-established fact that there are numerous plants used to derive hepato-protective medicines as they contain various kinds of phytoconstituents like polysaccharides, proteins, flavonoids, lignans, and rotenoids etc which enhanced the immune system and are involved in treating different hepatic diseases. The herbal plants are less expensive and have fewer side effects.[4] The mechanisms used to protect liver are degeneration of free radicals by increasing antioxidants.[5,6] Tecomellaundulata is a member of family Bignoniaceae. It is a flower grown on a small tree mostly in Saudi Arabia, Northwest of India and Southern Pakistan.[7] Locally it has given various names like Roheda, Lohira, Rohira and Purpak in different regions of Pakistan. In Pakistan it is found in Khuzdar, Baluchistan.[8-10] Whole plant including bark, seeds, roots, and flowers are used in treatment of various ailments. The flower is mostly used for treatment of hepatitis and seeds for abscess treatment.[11-13] Flowers of this plant are rich in Quercetin, Rutin and â- sitosterol.[14-16] The liver has various functions in body like metabolism of drugs, removing toxic material from body, vitamin storage, protein formation and lipid synthesis.[17] The liver can be damaged by hepatocellular injury, cholestatic damage and mixed injury in which alkaline phosphatase (ALP) is increased. The risk factors for liver injury are alcohol consumption, smoking, genetic and drug toxicities.[18] Isoniazid is the first line of therapy for treatment of tuberculosis. It is a prodrug with oral dosage of 10-15 mg/kg/day in children while, in adults it is 300mg/day.[19] Although the toxic dose in rats is 200 mg/kg body weight.[20] Isoniazid is an inactive drug that is activated by enzyme catalase peroxidase. The

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Received: 20-11-2019
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bacterial catalase peroxidase enzyme is secreted by mycobacterium tuberculosis. The active form of drug reduces nicotinamide adenine dinucleotide (NADH). This inhibits formation of mycolic acid in mycobacterium, which is a pivotal cell wall component.[21] The oral absorption of drug is rapid, and it diffuses well in all body fluids and tissues. According to authors knowledge; there is no literature available to treat the liver toxicity with herbal option in Pakistan and indeed it was the rationale of the study. Therefore, this study was aimed to evaluate the levels of liver enzymes and LFTs in rat models receiving Tecomellaundulata stem bark extract on liver toxicity induced by isoniazid and to evaluate the histopathology of liver after using Tecomellaundulata on isoniazid induced liver toxicity rats.

METHODOLOGY:

It was an experimental study; carried out in the Department of Pharmacology at Al-Tibri Medical College and Hospital, Isra University Karachi Campus and Dow University of Health Sciences, Karachi. The duration of the study was seven months from May 2018 till November 2018.This study had adult male albino wistar strain rats as experimental model selected from the animal house of Al-Tibri Medical College and Hospital Karachi. All animals were kept under standard laboratory conditions at temperature 27±2 °C and light and dark cycle 12/12 hour. The animals were fed on standard laboratory feed and water. Total twenty-four rats were studied. The rats that were male, healthy, albino, weighting 200-250grams were included in this study. The rats that were female, unhealthy or less than 200grams in weight were excluded from this study. The rats were divided into four groups having six rats in each group. These groups were A, B, C and D. the group A was control group, it had rats that were treated with normal animal diet and water orally for 30 days. The group B was Isoniazid treated group, in this group the hepatic injury was induced by oral administration of Isoniazid (INH) 50mg/kg once daily for 30 days. The group C was Isoniazid 50mg/kg and Tecomellaundulata bark extract with low dose, in this group Isoniazid 50mg/kg and Tecomellaundulata stem bark extract 200mg/kg were given orally once daily for 30 days. The group D was Isoniazid 50mg/kg and Tecomellaundulata bark extract with high dose, in this group Isoniazid 50mg/kg along with Tecomellaundulata stem bark extract i.e., 400mg/kg once daily per oral for 30 days. All the animals were weighed before commencement of the study. The animals were kept in separate cages. Two rats in each cage. The animals were given free access to diet and water and libitum. The animals were acclimatized to expose 12-hour light and 12-hour dark circadian cycle. The animal's condition and health were accessed by the gain or loss of weight and weakness of animals. After 30 days the animals in these groups were sacrificed under anesthesia. Liver was exposed and preserved for histopathology and blood 3ml was drawn by cardiac puncture for biochemical parameters (liver enzymes) like Alkaline phosphates (ALP), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT)and bilirubin. The data was recorded on excel spread sheets and analyzed on SPSS version 20. Means and standard deviation (SD) were calculated for quantitative data and Kruskal Wallis Test was applied to compare the values among four groups and p value = 0.05 was considered as significant.

RESULTS:

While comparing the mean values of AST, ALT, ALP and GGT in all four groups group; the statistical significant difference ($p<0.001$) was found. The mean levels in of total Bilirubin in group A was 0.69 ±0.01, group B 1.04 ±0.04, in group C was 1.15 ±0.39, and in group D was 1.04 ±0.44 with the significant difference ($p=0.004$).The mean levels in of direct Bilirubin in group A 0.02 ±0.01, group B 0.75 ±0.04, in group C was 0.80 ±0.07, and in group D was 0.47 ±0.23 with the significant difference ($p<0.001$). (Table: I)

DISCUSSION:

In our study the plant Tecomellaundulata (RohitakaGhrita) showed a protective effect on isoniazid induced liver injury on rat models. There was a protective effect of this herb on liver in paracetamol induced liver injury.[22] This plant was suggested to cure liver diseases at dose of 3.6gm/kg in a study.[23] In a recent study there was a hepatoprotective effect of plant Tecomellaundulata against liver injury.[24] It is a well known way to produce liver damage in rats by medicines;[25] there is marked increase in SGPT and SGOT levels that are released into systemic circulation due to hepatic cellular membrane damage. However, Tecomellaundulata reduces these levels markedly. The intoxication facilitates the release of alkaline phosphatase due to hepatic damage and it was remarkably reversed by Tecomellaundulata. Therefore, the decline in level of enzymes indicate membrane stabilizing role of Tecomellaundulata. In addition, the increase in serum bilirubin levels is a predictable way of assessing liver damage which was markedly decreased by Tecomellaundulata showing its efficacy as hepato protective agent. The free radical generation is thought to cause lipid peroxidation, depletion of glutathione and catalase[26] which is consistent with our study in which we also observed the protective effect. However, the study states that treatment with Tecomellaundulata can markedly restore the defense mechanism by increasing glutathione, catalase and hence decreasing peroxidation of cellular membrane. The results of our study outcomes were congruent with the another study in which prominent improvement was noted on histopathology of rats receiving Tecomellaundulata in toxicity induced by paracetamol, there was a hepatoprotective effect of Tecomellaundulata on hepatic tissue in other study.[22] Considering the views of our study and to what extent the levels of enzymes in these rats are associated with the

Table I: Levels of liver enzymes in various groups of Albino Rats

	Groups	Mean ± SD	Median (IQR)	p-value
AST	**A**	127.61 ± 1.94	127.39(125.86 – 129.52)	<0.001
	B	722.86 ±2.54	723.04(720.30 – 724.96)	
	C	350.46 ±1.59	349.99(349.06 – 352.13)	
	D	160.46 ±1.03	160.41(159.73 – 161.25)	
ALT	**A**	35.82 ± 2.03	35.51 (34.43 – 37.55)	<0.001
	B	91.59 ± 1.61	91.46 (89.96 – 93.11)	
	C	80.76 ± 1.95	80.40 (78.96 – 82.44)	
	D	49.39 ±1.42	49.74 (48.42 – 50.30)	
ALP	**A**	130.60 ± 1.21	130.48 (129.63 – 131.87)	<0.001
	B	271.18 ± 1.66	271.04 (269.70 – 273.02)	
	C	216.26 ± 2.08	216.46 (214.52 – 218.13)	
	D	178.91 ± 2.24	179.51 (176.61 – 180.97)	
GGT	**A**	8.95 ± 0.34	9.00 (8.80 – 9.14)	<0.001
	B	38.05 ± 2.21	38.01 (35.88 – 40.25)	
	C	29.43 ± 1.70	29.29 (28.32 – 31.08)	
	D	14.76 ± 1.23	14.96 (13.71 – 15.45)	
Total Bilirubin	**A**	0.69 ±0.01	0.69 (0.67 – 0.71)	0.004
	B	1.04 ±0.04	1.06 (0.98 – 1.06)	
	C	1.15 ±0.39	1.00 (0.98 – 1.25)	
	D	1.04 ±0.44	1.06 (0.98 – 1.06)	
Bilirubin Direct	**A**	0.02 ±0.01	0.02 (0.02 – 0.04)	<0.001
	B	0.75 ±0.04	0.75 (0.71 – 0.79)	
	C	0.80 ±0.07	0.83 (0.77 – 0.85)	
	D	0.47 ±0.23	0.47 (0.44 – 0.49)	

histological findings of the liver will be useful to discover more facts about the plant. The limitations of our study included measurement biases or observer bias and was conducted on small scale and hence results cannot be projected on general population. It is recommended that Tecomellaundulata is medicinally and economically important tree of arid regions of India and Pakistan. Due to its increasing demand in timber and pharmacological industry it is becoming extinct. The tree is grown slowly through seeds and there is no alternate method for its quick breeding. There is great need to preserve, reproduce and protect it so its beneficial medicinal uses can be sustained and available for prompt treatment of liver toxicity.

CONCLUSION:

Tecomellaundulata has a protective effect on isoniazid induced toxicity on liver as evidenced by liver function test on rat models. It was also predicted that in liver-injury induced rats, Tecomellaundulata can reverse the toxicity caused by isoniazid to the liver and thereby improving the overall status of liver enzymes.

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019073

Comparison of Cognitive-Affective Symptoms of Depression Between Cases of Low and High Suicidal Ideation in Medical Students

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ABSTRACT

Objective: To compare the severity of cognitive, affective and somatic symptoms of depression between two samples of medical students with high and low suicidal ideation using Beck Depression Inventory

Study Design and Setting: This is a cross sectional study conducted in public and private medical colleges in Karachi from September-December 2018.

Methodology: A total of 150 normal healthy students with 75 each from public and private medical colleges in Karachi were sampled through purposive sampling technique. Beck depression inventory (BDI) with twenty one items for depressive symptoms was used. Suicidal ideation was assessed using item 9 of BDI and participants were identified as having high and low suicidal ideation. Remaining twenty items of BDI were categorized as affective, cognitive and somatic symptoms of depression. Severity of each symptom was assessed through BDI score on a 4-point scale. Hypothesis testing for difference in BDI scores of depressive symptoms between high and low suicidal ideation cases was performed through independent sample t tests.

Result: BDI showed significantly higher suicidal ideation in public medical colleges' students. Cases with high suicidal ideation showed higher prevalence of five cognitive (past failure, feeling guilty, self-image, feeling of being punished, crying spells), four affective (sadness, irritability, decision making, self-dislike) and one somatic (physical health) symptoms of depression.

Conclusion: Significant higher prevalence of affective and cognitive symptoms of depression was found among cases of higher suicidal ideation.

Keywords: BDI, Cognitive affective symptoms, Medical students, Suicidal ideation.

INTRODUCTION:

Cases of suicidal ideation and suicidal behavior are growing among youth particularly among medical students[1]. Prevalence rate reported in literature for suicidal ideation is as high as 53.6% indicating the gravity of the situation[2]. Many factors have been associated with this grave illness, however, history of familial or non-familial psychiatric illness, loneliness, lack of social support, financial problems, problematic childhood, lack of parental care, abusive relationships and post-traumatic stress disorder (PSTD) are suggested as strong indicators of suicidal ideation which may end up in suicidal attempts or other suicidal behavior[3,4,5,6].

Suicidal ideation is thought to be the preliminary step towards suicidal behavior[7]. Suicidal thoughts are considered as a persistent illness rather than an acute crisis. Therefore identification of associated risk factors for suicidal ideation and understanding the link between suicidal ideation and suicidal behavior is very important in order to design a preventive strategy against this growing illness.[8,9] For this purpose research studies investigating suicidal ideation played a key role to understand this complex mental health issue.

Beck Depression Inventory, a self report measure is frequently used for the assessment of depression and depressive symptoms both in psychiatric and non-psychiatric healthy population[10]. BDI contains twenty one items which measure affective, cognitive and somatic symptoms of depression[11]. Affective symptoms of depression included in BDI are sadness, dissatisfaction and boredom, self-dislike, irritability, loss of interpersonal interest, indecisiveness. While cognitive symptoms included in BDI are pessimism, past failure, feeling guilty, feeling of being punished, self-blame, suicidal ideation, crying spells, self-image. Somatic symptoms included loss of working capability, sleep disturbance, physical energy, loss of appetite, However the validity of BDI as depicted by Cronbach's alpha is high for psychiatric patients than non-psychiatric healthy population[12]. Somatic symptoms of depression has been linked to diseases like

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Received: 09-07-2019
Accepted: 15-11-2019

heart failure, myocardial infarction and some metabolic syndromes[13,14,15,16].Higher prevalence of somatic symptoms were also found in elderly population[17,18] and female gender[19]. Some studies also revealed association of affective and cognitive symptoms with physical morbidity, however, somatic symptoms override cognitive and affective symptoms in such cases.[20, 21] Somatic symptoms like insomnia, lack of physical energy, insomnia, fatigue, weight loss have been linked to depression and suicidal ideation.[9] Cases with high suicidal ideation have also showed impairments in cognitive control[22], that is they are unable to control their feelings and thoughts in order to understand the changes in environment and to cope with these changes. This impairment becomes pronounced when the environment is complex, challenging or ambiguous[23].

Most of the depressive symptoms associated with suicidal ideation and suicidal behavior are affective and cognitive in nature[11]. Somatic factors like insomnia, fatigue etc are also commonly expressed through affective or cognitive symptoms. It was hypothesized that **t**here is no significant difference in the prevalence of affective, cognitive, and somatic symptoms of depression between cases of high and low suicidal ideation. The current stud aimed to compare the prevalence of affective, cognitive and somatic symptoms using Beck Depression Inventory among cases of low and high suicidal ideation.

METHODOLOGY:

It was a cross sectional study conducted among third year medical students of public and private medical colleges in Karachi. The study participants were selected through purposive sampling technique. This study was approved by Ethical Review Board of Virtual University and Karachi Institute of Medical Sciences. Sample size was calculated using methodology given in Naing et al[24]and at prevalence rate of 21%[25] as 254. Due to resource constraints 150 students were part of the study. Medical students of third year MBBS from both the genders and age between 18-24 years and healthy individuals were included in the study. All the cases with personal or familial history of psychiatric illnesses were excluded. Before giving the BDI the informed and written consent was obtained from the participants. Beck Depression Inventory was used to estimate the level of suicidal ideation and other depressive symptoms among medical students. Suicidal ideation among medical students was assessed using item 9 of BDI on 4-point scale ranging from 0-3, where 0 means no suicidal thoughts and 3 means most severe suicidal thoughts. All other symptoms were also assessed on the same 4-point scale. Depressive symptoms were distributed into somatic, cognitive and affective categories as given in various studies.[11, 21] SPSS version 16 was used for data analyses and p-value <0.05 was considered as statistically significant. Independent t-tests was used to find out significant differences between the cases of high and low suicidal ideation across all the affective, cognitive and somatic depressive symptoms included in BDI. On the basis of BDI scores students from Public and Private medical colleges were now identified as cases of high and low suicidal ideation respectively.

RESULTS:

Suicidal Ideation was found in 58% students of public medical colleges and only 11% of private medical colleges. Therefore samples from public medical colleges were identified as high suicidal ideation cases and those from private medical colleges as low suicidal ideation cases. BDI scores were calculated for each of the twenty items each of which depicted the severity of depressive symptoms on 4-point scale ranging from 0 to 3. BDI scores of high and low suicidal ideation cases differ across twenty items of Beck Depression Inventory- (Fig-1). This difference in BDI score was as high as 46 for working capability and 44 for crying spells to as low as 3 for loss of appetite.

Table 1 shows the items of BDI that were significant differences in BDI score between cases of high and low suicidal ideation.

DISCUSSION:

Depression is one of the major public health issues particularly of young students. Its prevalence rate is growing over the last two decades. Suicidal ideation is one of the major threatening symptoms of depression. According to World Health Organization suicide is the second leading cause of death among 15-29 years old. Variation reported in prevalence rate of depression and suicidal ideation in different studies can be attributed to differences in sample sizes, sampling area, study design, instrument or questionnaire used. Suicidal ideation is the most threatening symptom of depression that may lead to suicidal attempts and suicidal behavior. In our study the suicidal ideation was found in 58% and 11% students of public and private medical colleges respectively. On the other hand prevalence of sucidal ideation for medical students in Pakistan are as high as 31.4%. The difference in rates of suicidal ideation may be atributed to factors mentioned above[26]. Owing to its fatal consequences suicidal ideation must be investigated extensively so that prevention and intervention can be made promptly and properly. Although worldwide incidence rate of suicide is 800,000, Pakistan has a lower rate of suicide which may result from under reported incidents, lack of research, or its status of being an offence in Pakistan Penal Code.[27]

The age shift of depression and suicidal ideation from elderly people to young generation was reported recently. Academic stress, family problems, financial stress, and competitive environment are held responsible for this illness[6]. In the context of Pakistan, a particular aspect of suicidal ideation and behavior is related to religion. Suicidal behavior is strictly prohibited in Islam. In spite of this religious prohibition prevalence is growing day by day showing the gravity of the problem and need for intervention through

Fig- 1: BDI scores of depressive symptoms across high and low suicidal ideation cases of the present study.

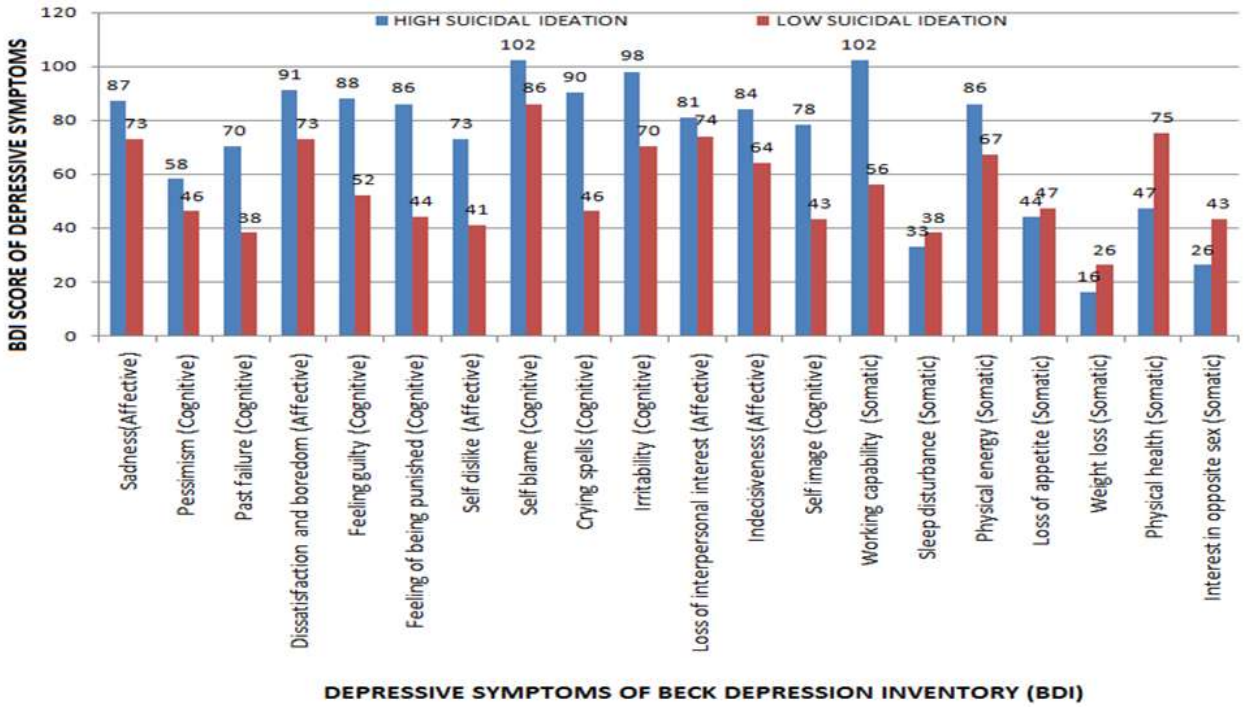

Table-1: Independent sample t tests showed significant differences (p value <0.05) in the prevalence of affective, cognitive and somatic symptoms between cases of high and low suicidal ideation.

BDI Item No.	Depressive symptoms included in Beck Depression Inventory (BDI)	t value	Degree of Freedom	P-Value
1	Sadness	2.20	148	0.03
3	Past failure	2.74	148	0.01
5	Feeling guilty	3.87	148	0.00
6	Feeling of being punished	2.86	148	0.01
7	Self-dislike	2.88	148	0.01
10	Crying spells	3.98	148	0.00
11	Irritability	2.38	148	0.02
13	Indecisiveness	2.12	148	0.04
14	Self-image	2.15	148	0.03
15	Working capability	4.69	148	0.00
20	Physical health	-2.68	148	0.01

proper planning, research and collaborative efforts from all stake holders. For example, studies with a sample sizes ranging from 195 to 114 participants showed suicidal ideation as high as 38.7% (in Saudi Arabia) to as low as 17.5% (in Egypt)[25]. It shows that religious beliefs make a little difference in suicidal ideation and it should be dealt with a broader perspective taking all the relevant factors into account. Prevention and intervention to this morbid illness need proper diagnosis. Health care professional must know that a patient showing depressive symptoms is vulnerable to develop suicidal ideation. Alarming symptoms and signs should be observed cautiously and must be investigated extensively through self-report measures, case history and in depth interviews. Some of the depressive cases report severe somatic symptoms and some are victims of cognitive and affective deterioration. However, studies revealed that patients who develop depression after a physical morbidity or illness are more likely to show somatic symptoms. These patients belong to elderly age group when physical illnesses are more common occurrence. Adolescents and young adults are more likely to develop affective and cognitive symptoms that usually precede the occurrence of full blown depression[28]. It is worth mentioning that cognitive symptoms are becoming the focus of interest for psychiatric illnesses other than

depression like schizophrenia, bipolar disorders, etc.[29,30] However; there is a dire need for exhaustive research to declare cognitive symptoms and dysfunction as causative factors or even risk factors for full blown depression, nevertheless association was revealed in various studies[31]. Cognitive and somatic symptoms have also been used for predicting biological changes in depression, reflecting the importance of assessing and diagnosing these symptoms in cases vulnerable to develop depression[32]. This study emphasized the importance of depressive symptoms and their distribution into somatic, cognitive and affective categories as the clinical picture of depression may vary with predominance of one or two of the three categories of depressive symptoms. Early intervention and preventive measures are likely to be more focused if the target groups can be identified and stratified according to the symptoms they predominantly present. As the suicidal ideation, the most threatening symptom of depression, is linked with suicidal behavior early diagnosis may help to reduce the suicide rates.

CONCLUSION:

Medical students were found more vulnerable to develop depressive symptoms. Significant higher prevalence of affective and cognitive symptoms of depression was found among cases of higher suicidal ideation.

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Original Article DOI: https://doi.org/10.51985/JBUMDC2019104

Comparison of Triamcinolone Versus Platelet Rich Plasma Injection for Improving Trismus in Oral Submucous Fibrosis

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ABSTRACT:

Objective: To compare the effect of Triamcinolone versus Platelet Rich Plasma (PRP) injection intraorally for improving trismus in Oral Submucous Fibrosis (OSMF).

Study Design and setting: Randomized double-blind comparative study, conducted at ENT department of PNS Shifa Hospital, Karachi from 1st June 2015 to 30th June 2016.

Methodology: Eighty patients with trismus due to oral submucous fibrosis were divided randomly into two groups, 'A' and 'B' of 40 patients each. In Group A, Inj. Triamcinolone 40mg (1 ml) was injected into the sub-mucosal plane in the retro-molar trigone area and into the fibrous bands along the soft palate on multiple sites, weekly for 6 weeks. In group B Inj. PRP 1ml weekly was administered for 6 weeks along the same site. Vernier calipers were used to precisely measure the Maximum Interincisal Distance (MIID) in cms before and after the treatment.

Result: There was a male preponderance in the study group with a male to female ratio of 5.1:1. In group 'A' mean pre-treatment MIID was 2.3±0.7 cms, while in group 'B', it was 2.2± 0.5 cms. After completion of 6 weeks treatment the mean MIID improved in group 'A' to 3.08 ± 0.8cms, and in group 'B' to 3.22± 0.5cms. The mean improvement in MIID in group 'A' was 0.783± 0.25cms compared to 1.01± 0.05 cms in group 'B' ($p < 0.05$).

Conclusion: Intraoral injection of PRP is more effective than Triamcinolone in improving trismus due to OSMF.

Key Words: Injection, Oral Sub Mucosal Fibrosis, Platelet rich Plasma, Trismus, Triamcinolone.

INTRODUCTION:

Oral sub mucous fibrosis (OSMF) is a potentially malignant condition of the oral cavity resulting in increasing loss of tissue mobility, marked rigidity and an eventual restricted ability to open the mouth. It may progressively affect the entire oral cavity, and occasionally the pharynx, causing a gradual reduction in mouth opening. It's association with other premalignant conditions like leukoplakia and lichen planus has also been noted. There is a considerable variation in its rate of transformation to malignancy, ranging from 3% to 19%[1,2]**.** The pathogenesis of OSMF is complex and incompletely understood. It has a strong link to areca nut (betel nut) chewing. The other proposed etiological factors include excessive chilly consumption, vitamin B12 and iron deficiency, tobacco ingestion, smoking, autoimmunity, genetic and environmental factors[3,4,5].

The disease begins with vesicle formation, followed by inflammation and increasing hyalinization of the lamina propria. This results in extensive fibrosis of the subepithelial as well as submucosal tissue which represents as thick, vertical bands in the cheeks, faucial pillars and even surround the lips causing trismus and difficulty in protrusion of the tongue. The blanching of oral mucosa is due to impaired local vascularity, imparting it a marble like appearance[6]. The most commonly involved site is buccal mucosa, followed by palate, retro molar region, faucial pillars and pharynx[7]. Consequently, in advanced stages, OSMF leads to dysphagia and difficult phonation. The resultant limited access to the oral cavity eventually causes malnutrition and poor oral hygiene. The severity of trismus can be graded by measuring the distance between the upper and lower incisors while the mouth is opened to the maximum. The mouth opening is categorized into stage I (>3 cm), stage II (2–3 cm), and stage III (<2cm)[8,9,10]**.**

Treatment of oral submucous fibrosis is based on medical and surgical management along with physiotherapy. Conventional medical management includes avoidance of

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Received: 25-09-2019
Accepted: 30-12-2019

irritating substance like betel chewing, tobacco ingestion or smoking etc. and involves regular administration of corticosteroids, either via submucosal injections or topical application. Steroids, in addition to inhibition of production of phospholipase A2; resulting in reducing the production of prostaglandins and leukotriene, stabilize lysosomal membranes and prevent the release of proteolytic enzymes as well. Several glucocorticoids are used for the treatment of OSMF such as short-acting (hydrocortisone) intermediate acting (triamcinolone), and long-acting glucocorticoids (betamethasone and dexamethasone)[11].Recently platelet-rich plasma (PRP) treatment is gaining popularity in oral and dental surgery[12,13]. Its use in alleviating trismus in OSMF however hasn't been published. Platelet-rich plasma is the autologous component of the plasma and contains higher concentrations of platelets, growth factors, and cytokines than the basal levels[14].Platelet rich plasma is an element of whole blood, prepared through centrifugation to a concentrated form. It is processed with an activating agent and then finally injected into the oral submucosa. Platelet rich plasma acts by inducing the platelets to secrete pro-inflammatory mediators and growth factors. These, in turn, initiate the cascade of wound healing and bring about tissue remodeling. It was suggested that the acceleration of the process of wound healing by PRP depended on the synergistic effects of these growth factors.

The effectiveness of triamcinolone acetonide versus platelet-rich plasma in improving trismus is not documented in local literature. Our study is a pilot study which sets out to determine which treatment is more efficacious in effectively improving trismus due to oral submucous fibrosis.

METHODOLOGY:

This study was conducted at the department of Otorhinolaryngology, Head & Neck surgery, PNS Shifa Hospital, Karachi, over a period of one year from June 2015 to June 2016. After obtaining ethical clearance for the study from the Hospital Ethical Committee, each patient included was informed about the treatment protocol and informed consent was obtained. Consecutive convenient sampling technique was employed and a total of eighty patients were included for this study. The patients included in the study were of either gender, of any age, with a clinical diagnosis of OSMF, having burning sensation on eating spicy food, presence of palpable fibrous bands on the soft palate and having restricted mouth opening. The exclusion criteria were those who had undergone any other treatment for OSMF, those with temporo-mandibular joint disorders, any systemic disease, those who were allergic to local drugs, those with trismus due to other causes and those with other pre-malignant lesions like leukoplakia.

This was a double-blind study where not the patient and nor the performer were aware of the group. Patients were randomly divided in to two groups, 'A' and 'B' of 40 patients each. In group A, injection Triamcinolone 40mg (1 ml), filled in an insulin syringe, was injected intraorally in the sub mucosal plane, into the retro-molar trigone and in the fibrous band along the soft palate on multiple sites, weekly for 6 weeks. Patients of group B were administered Inj. PRP (1ml) weekly for 6 weeks along the same sites. The MIID was precisely measured with a Vernier calipers initially, before commencing the treatment, and subsequently on all visits. Following the completion of treatment these patients were followed up monthly for a period of 9 months. Enquiry about symptomatic subjective improvement was done and precise documentation of MIID was carried out in all these visits. Data was entered and statistical analysis was done using the SPSS version 23 and a p-value of less than 0.05 was considered significant.

RESULTS:

A total of 80 patients included in our study and divided randomly into two groups; 'A' and 'B', consisting of 40 patients each. Overall, there were 67 males and 13 females in total study group, with a male to female ratio of 5.1:1. The male preponderance was evident in almost the same ratio in both groups; 33 males and 07 females in Group 'A', and 34 males and 06 females in group 'B'. The mean age of total patients was found to be 24.65 ± 4.6 with a minimum of 16 and maximum of 37 years. In Group 'A' the age ranged from 16 to 37 years with a mean of 24.38 ± 4.9 years. In Group B the age ranged from 18 to 33 years with a mean age of 24.93± 4.3 years.

All patients had a positive history of using areca nut ('Chaliya' or 'Supari') either alone or in different combinations including Gutka and Paan. Betel nut alone was used by 36 patients (45%) followed by 'Gutka' in 29 patients (36.2%) and pan in 15 patients (18.8%) (Fig 3).In group A, 19 patients (47.5%) were using betel nut alone, 14 (35%) using Gutka and 7 (17.5%) were eating Paan. In Group B, 17 patients (42.5%) were using betel nut, 15 (37.5%) Gutka and 8 (20%) were eating Paan. These patients were using these substances from 6 months to 20 years with a mean time duration of 7.725 ± 3.7 years. In group A the mean duration of use was 8.07 ± 4.7 years (0.5 to 20 years), while in Group B it was 7.38 ±2.58 years (3 to 12 years).66 patients (82.5%) had stopped taking these substances with the mean duration of stopping was 88.75±29 days. Surprisingly 14 patients (17.5%)has not stopped taking these substances, with a count of 7 patients in each group.

In group 'A' mean pre-treatment MIID was 2.3±0.7 cms, while in group 'B', it was 2.2± 0.5 cms. After completion of 6 weeks treatment the mean MIID improved in group 'A' to 3.08 ± 0.8cms, and in group 'B' to 3.22± 0.5cms. The mean improvement in MIID in group 'A' was 0.783 +/- 0.25cms compared to 1.01 +/- 0.05 cms in group 'B'. The resultant P value was 0.0124 which is statistically significant.

Fig 1: Etiological factors of OSMF

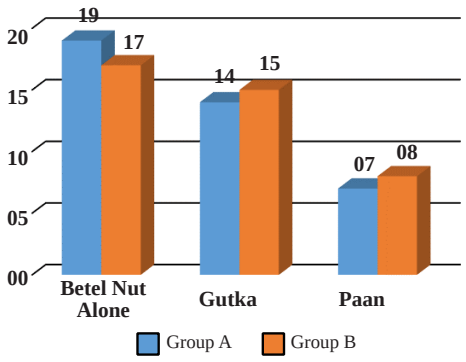
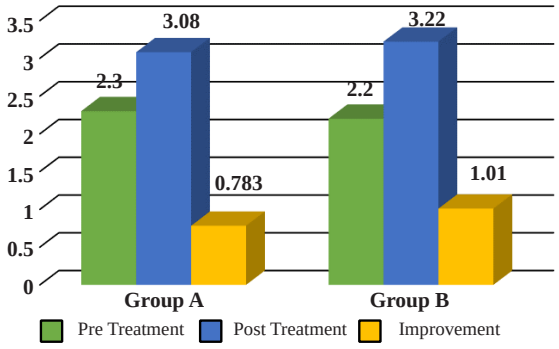


Fig 2: Pre and post treatment MIID readings with Mean Improvement in centimeters in both groups.



DISCUSSION:

Over the last 2-3 decades there has been an exponential increase in the manufacturing of attractive areca nut products, Gutka or Paan Masala with an escalating consumption in the younger generation, ultimately leading to an increased incidence of OSMF[15].There is a multitude of non-surgical methods of management of OSMF. They include Corticosteroids, Proteolytic enzymes, Vitamins, Levamisole, Placental extract, Interferon-Ý, peripheral vasodilators and ayurvedic medicines[16]. Many studies have used various combinations of either short acting, intermediate or long acting steroids with hyaluronidase[17]. Generally, a review of published studies reveals a male predominance[18,19,20] except one odd study with opposing results[16]. In a study conducted in Karachi Pakistan, male to female ratio was found 7:1 showing the male preponderance in this group of Pakistani population[21]. This is commensurate with the findings of 5.1:1 in our study.

Patients using areca nut products are generally young adults, as evinced in a study from Allahabad, India, where 46%patients were in their 3rd decade of life[7].This is similar to the findings of our study where the mean age was 24.65 years. According to a study conducted by Hazarey et.al[22] 77.8% patients were consuming multiple products, whereas 20.5%, patients were having oral consumption of a single product. Mean duration of substance abuse was 1.4 ± 3.59 years. This is in contrast with our study where only 17.5% (n=14) patients were consuming multiple products. While mean duration of coral consumption was 7.7 (3.7) years.

Injection Triamcinolone proved to be superior to placental extract[23] and Dexamethasone[24] but when compared with other preparations like oral colchicine[25] and Lycopene[26] failed to give fruitful results. Platelet-rich plasma (PRP) is a new approach to tissue regeneration and it is becoming a valuable adjunct to promote healing in many procedures in different fields of medicine and surgery. PRP was first used in 1987 by M. Ferrari after an open-heart surgery[27.] Now, it is widely used in various fields of medicine and surgery including plastic surgery, otorhinolaryngology, neurosurgery, urology, dermatology, general surgery, gynecology and obstetrics. In 1997 Whitman et al presented the use of PRP in oral surgery. This biological treatment mimics the natural pathways of wound healing by driving to the injury site the whole protein array of PRGF (plasma rich in growth factors) to repair the damaged tissues, thus it accelerates bone repair, promotes fibroblast proliferation, and increases tissue vascularity[28]. PRP has a platelet concentration above baseline. Normal platelet counts in blood range between 150,000/µl and 350,000/µl and average about 200,000/µl but according to scientific proofs PRP provides up to 1,000,000 platelets/µl locally, in a 5-ml volume of plasma which is the working definition of PRP today[29], thereby increases the concentration of growth factors and platelets by 5 to 10 times the normal amount. A small amount of patient's blood is drawn i.e. up to 20-50cc and sent to the laboratory for processing in centrifuge machine. Before applying injections, topical anesthesia is given, although it is a mild procedure but some patients might complain of slight discomfort to burning sensation at the site of needle prick. Being autologous, it is free from hazard of allergic reactions or transfer of contagious diseases.

A review of medical literature reveals that to date there is no published study either documenting the use of PRP in managing OSMF nor comparing its effect with intralesional steroids. Although there are no similar studies, yet a fair idea of improvement in MIID can be gauged by comparing the results of different studies. Regarding PRP, in dentistry several studies have been done for treatment of chronic inflammatory diseases and those which aid in bone regeneration in postoperative cases of alveolar or jaw diseases. In otorhinolaryngology, use of PRP as a biological graft material for repair of tympanic membrane perforation, was used which gave 100% success rate. An improvement in MIID of 4.3±0.8mm, after biweekly Injections of 1.5ml Dexamethasone and 1500 I.U Hyaluronidase for 6 weeks;[30] 6±2 mm after biweekly Injections of 1.5ml Dexamethasone and 1500 I.U Hyaluronidase for 4 weeks[18], 9.38mm after 8 weeks treatment of intralesional Hyaluronidase injection[19],

3.13mm after 4 mg Injection Dexamethasone and 1500 I.U Hyaluronidase weekly injections for 12 weeks[20]. Finally, 3.9 mm improvement in MIID was seen after 4mg (1ml) Injection Betamethasone twice weekly for 8 weeks[26]. Thus, the maximum improvement was 9.38mm. This is in similar with the results of our study where the mean improvement in MIID in group 'A' was 7.83 +/- 0.25mms compared to 10.1 +/- 0.05 mms in group 'B'.

The limitations of this study is definitely small number of cases, but it is a pilot study where more cases and experience is required in future. Similar studies are also required to be carried out in other centers of Pakistan to compare the results. Although PRP is very effective but its cost, the trauma and hassle of withdrawing blood on every visit and the wait till the blood is centrifuged and prepared are limiting factors.

CONCLUSION:

Intraoral injection of platelet rich plasma was more effective than Triamcinolone in improving trismus due to OSMF, however larger studies are required to corroborate these findings.

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Student Corner - Original Article DOI: https://doi.org/10.51985/JBUMDC2019114

Association Between Delayed Diagnosis Of Breast Cancer And Its Degree Of Invasiveness Among The Patients In Tertiary Care Hospital Of Karachi

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ABSTRACT

Objective: To find the association between delayed diagnosis of breast cancer over the degree of invasiveness for each of the immune-histochmically defined molecular type of invasive ductal carcinoma among the patient in tertiary care hospital of Karachi.

Study Design and Setting: A cross sectional study was conducted on 153 post mastectomy patients in a time frame of two years at Bait-ul-Sukoon Hospital who had their immunohistochemistry workup.

Methodology: The patients included in the research were diagnosed cases of breast cancer; had post-mastectomy with their histopathological and immunochemistry status work up reports. In addition to demographic variables; the histopathological report of specimen, histological tumor type and grade, invasive tumor size, axillary lymph node status, Paget's disease and stage of the disease were recorded from the histopathological report however ER, PR and Her 2 neu receptor statuses were confirmed via immunochemistry report. Volume of the tumor was calculated using the following formula $V = (W^2 \times L)/2$ Convenient sampling was applied and the data was analyzed on SPSS 20.0 with CI-95% and P=0.05.

Results- All 153 patients reported because of unpleasant symptoms.47.1% of the participants presented with LT while the remaining 52.9% were grouped as NLT. The association of molecular type with stage at mastectomy was statistically significant (P=0.015) in the ERG. Her-2 enriched variant shows that there was a moderate positive statistically significant relationship between log of total delay and log of tumor volume +2.

Conclusion: Delay in diagnosis due to lack of screening modalities, lesser awareness among low socioeconomic groups and inaccessibility to tertiary care were not the major causes of aggressive tumors at diagnosis in developing countries, instead all the major known risk factors influence to the tumor burden collectively .

Keywords: Breast Carcinoma, Delayed diagnosis, Immunohistochemistry, Invasiveness, Post mastectomy.

INTRODUCTION:

Breast carcinoma is one of the most prevalent forms of neoplastic tissue growth amounting for 23% of diagnosed carcinoma and 14% of deaths among women of all ages and ethnicities across the world.[1] As per to the data available, 1.7 million cases were reported in the year 2012 with a 35.5% rise in mortality rate from 2000-2011.[2, 3] In the recent years breast carcinoma is proving to be the commonest female malignancy in the developing Asian countries, despite the prevalence being lower in Asian region than compared to the Western developed countries, the mortality rate are disproportionately higher.[4, 5, 6] According to latest statistical reports carried out in 2015, Pakistan is emerging as Asia's hub with 2.5 time higher incidence, 1 in 9 women during their life time develop breast carcinoma.[7, 8]

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Received: 15-10-2019
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A significant contributing factor to the breast cancer deaths globally is delay in the diagnosis, which comprises of two parts; patient delay and medical system delay.[9, 10] The delay itself is multifactorial which is observed due to lack of female awareness regarding the presentation of the disease, poverty, poor access to health care facility, widespread illiteracy, cultural stigma, lack of resources to offer screening programs and limited amount of human expertise.[11,12,13,14]

Staging of breast carcinoma is a process to find out the invasiveness and spread of the cancer within the normal tissue. According to American Joint Committee on Cancer (AJCC) the TNM system is implemented to stage breast cancer,[15, 16] which comprises of

1- T- primary tumor size,

2- N- lymph node involvement

3- M- Distant metastasis.

Specific combination of TNM invasion is grouped into 4 classes from I-IV. With I being the least invasive form and the IV the most highly invaded form.[16, 17]Highly invasive form confirmed by trucut biopsy at the time of diagnosis; and has the worst prognostic characteristics resulting in higher mortality rates for this disease.[18]

All the different histological and molecular classes of invasive adenocarcinoma shows unique growth pattern, proliferative rates, nodal involvement, distant metastasis and long term prognosis rate.[19, 20] This raises the great dilemma that whether

the diagnostic delay irrespective of the tumor's intrinsic makeup is the chief factor responsible for the advanced degree of invasive component of the tumor or presence of specific rapid proliferative morphological and molecular subtype is a must for highly invasive tumor masses. The effect of delay in diagnosis over the prognosis of the disease is controversial and cannot be studied in randomized controlled trails due to ethical regulations. Hence this study was designed as a retrospective study and was the rationale of study. This study was aimed to find the association between delayed diagnoses of breast cancer over the degree of invasiveness for each of the immune-histochemically defined molecular types of invasive ductal carcinoma.

METHODOLOGY:

This was a cross sectional study conducted at Bait ulSukun Hospital, Karachi, in a time frame of two years from July 2017 to July 2019. The patients included in the research were diagnosed cases of breast cancer; who had undergone mastectomy with their histopathological and immuno-chemistry status work up report. The subjects in the study were included after informed consent with no other added interventions except data collection keeping in mind the inclusion and exclusion criteria. The study was approved by the ethical review committee of Bahria University Medical and Dental College, Karachi. The demographics variables include age, ethnicity, education status, contact number, family history of breast cancer, and the ability to re-call the dates as to when the symptoms appeared, when the subjects presented to the clinic and when was a diagnosis made were documented in the questionnaire. Patients with neo adjuvant chemo or radiotherapy were not included in the study. From September'17 to September'18; total 320 women with diagnosed cases of breast carcinoma at Bait Us Sukoon Hospital were selected; from which 153 questionnaires were fully validated through initial hospital medical file survey supplemented with a phone call mediated structured questionnaire-based interview. In addition to demographic variables; histological tumor type and grade, invasive tumor size, axillary lymph node status, Paget's disease and stage of the disease were recorded from the histopathological report however ER, PR and Her 2 neu receptor statuses were confirmed via immunochemistry report.

Tumors were grouped according to their grading and immunohistochemistry microarray analysis; they were graded on the basis of glandular/tubular differentiation and nuclear pleomorphism, grade 1 being well differentiated whereas grade 3 being poorly differentiated. While, luminal molecular variant consisted of tumors labelled ER +ve, PR +ve /-ve, Her 2 +ve/-ve whereas non luminal variant consisted of basal (triple negative) variant with ER -ve, PR -ve and Her 2 -ve and Her 2 enriched variant with ER -ve, PR -ve and Her 2 +ve statuses.

Tumor with luminal molecular variant were grouped as luminal group while those with Her-2 enriched and basal molecular type were grouped together under the non-luminal category. Patients who took less than a year from recognition of symptoms to presenting in clinic and acquiring definitive surgical treatment were grouped as early report group (ERG) while those who took more than a year for the entire process were grouped as late report group (LRG).

Delay in the diagnosis, comprises of patient delay and medical system delay. Patient delay is the time span between the appearances of the first symptom/s to the first consultation with a medic whereas; the medical system delay being the time from first consultation to an exact diagnosis to the initiation of treatment. SPSS version 23 was used for data analysis and p-value <0.05 was considered statistically significaent. Chi square was carried out to asses association of stage at mastectomy to the molecular variant and total delay. Volume of the tumor was calculated using the following formula $V = (W^2 \times L)/2$. In order to satisfy the rule of normality Log (total delay) and log (Tumor volume+2) was also calculated. The assumption of normality was tested using Shapiro-Wilk test for normality and skewness. Pearson correlation analysis was carried out separately for all the three molecular variants to find out if there is any significant correlation between the two variables.

RESULTS:

Data concerning the demographic characteristics of the patients included in the study group and the tumor features are summarized in table 1. The participants included were in the age group of 26 to 70 years, with 45.8% being in the age band of 41 to 55 years. Almost a two third of sample size i.e. 74.4% were pre-menopausal. The laterality of the specimen was almost equal in the study as 47.1% of the patients had their right breast affected while the rest of 52.9% had the left breast involved. None of the subjects had any history of recurrent carcinomas.

Among the symptoms for which these women initially consulted a breast clinic, lump or a swelling in the breast was the most common as 90.2% sought consultation as a result of it. Among 87.6% of the subject the delay from recognition of symptoms to acquiring definitive surgical treatment was less than a year hence they were categorized as the early report group (ERG). 47.1% of the participants presented with luminal molecular pattern while the remaining 52.9% were grouped as Non-luminal molecular variant (HER-2 enriched and basal). Only 3.9% had stage I disease while the remaining 41.2% and 54.9% had stage II and III respectively. Similarly, only 1.3% presented with grade I tumor while the remaining 39.2% and 59.5% were grade II and III tumors respectively.

Table 2- shows crosstab to asses association between the stage of the mastectomy specimen with the molecular variant of the tumor, luminal and non-luminal (P= 0.089) and also with time delay until definitive surgical treatment, early report group and late report group (P=0.357). Furthermore,

Table -1 Demographic characteristics of patients and tumor feature

Parameter	Categories	Luminal (Non-Aggressive tumor type)	Non-Luminal (Aggressive tumor type) (Her-2 enriched and basal)	Total
Total frequency		72	81	153
Age	26-40 41-55 55-70	20 32 20	30 38 13	50 70 33
Ethnicity	Urdu Speaking Punjabi Sindhi Balochi Pakhtoon	54 9 2 3 4	62 6 3 8 2	116 15 5 11 6
Educational Status	Lower to intermediate Higher to Intermediate	61 11	61 20	122 31
Family History of Breast Cancer	Yes No	15 57	19 62	34 119
Specimen Laterality	Right Left	31 41	40 40	71 81
Histological Tumor Variant	Invasive Ductal Carcinoma Others	59 13	71 10	130 23
Stage	I II III	3 23 46	3 40 38	6 63 84
Grade	I II III	2 34 36	0 26 55	2 60 91
Paget's Disease	Yes No	16 56	13 68	29 124
Delay in Reporting	Within one Year More than one year	64 8	70 11	134 19

Table-2 Association between stage at diagnosis with molecular variant versus reporting delay

		Stage I	Stage II	Stage III	Total	P-values
Molecular variant	Luminal	3	23	46	72	0.089
	Non-Luminal	3	40	38	81	
	Total	6	63	84	153	
Reporting Delay	Within one Year	6	57	71	134	0.357
	More than one year	0	6	13	19	
	Total	6	63	84	153	

Table-3 Association of stage at diagnosis with molecular subtype in early versus late report group

		Stage I	Stage II	Stage III	Total	P-values
Within one year (ERG)	Luminal	3	19	42	64	0.015
	Non-Luminal	3	38	29	70	
	Total	6	57	71	134	
More than one year (LRG)	Within one Year	0	4	4	8	0.141
	More than one year	0	2	9	11	
	Total	0	6	13	19	

Table-4 Pearson correlation between (Log of tumor volume +2) and (Log of Total delay)

Log of Tumor Volume + 2		Log of Total delay	P-value
Luminal		0.035	0.385
Non-Luminal	Her-2 enriched	0.271	0.036
	Basal	0.211	0.108

a subgroup analysis of ERG versus LRG in order to assess any association of stage at mastectomy with luminal and non-luminal variant is shown in table-3. The association of molecular type with stage at mastectomy was statistically significant (P=0.015) in the ERG while it was not significant among the participants in the LRG (P=0.141)

Table-4 shows the results of Pearson correlation to assess statistically significant correlation between Log of tumor volume +2 and Log of Total delay for each molecular variant separately. The result for Her-2 enriched variant shows that there was a moderate positive statistically significant relationship between log of total delay (M=2.06, SD=0.41) and log of tumor volume +2 (Her-2 enriched variant) (M=1.48, SD=0.58) (r (43) =0.271, p<0.05), one-tailed. This relationship can account for 7.34% of variation of scores (R^2 =0.0734).

DISCUSSION:

Mammography is one of the screening modality that aids in identifying asymptomatic breast cancers, according to studies done in 2017-18, it was established that it has its advantage of reducing breast cancer mortality rate by 40% along with its limitation of having low sensitivity and specificity with increasing number of false positive results.[21]

However, in our study all 153 patients reported because of unpleasant symptoms instead of a prophylactic mammographic screening. Thus, due to lack of screening modalities in a developing country like Pakistan, It was hypothesized that delay in diagnosis substantially results in an advance stage of the disease. .

Early diagnosis and effective prompt treatment have been the core principles of oncology department, coherent with this a previous study conducted in Dalarna County, Sweden [22] has suggested that patients with shorter delay have less aggressive disease and better prognosis with 60% lower risk of dying from breast cancer within 10 years after diagnosis and 47% lower risk of dying from breast cancer within 20 years after diagnosis[25]. Consistent with our figures where 47% of patients in ERG presented with stage I/II disease while 0% and 31.6% of the LRG presented at stage I and stage II respectively, yet not statistically significant (P=0.357).

Similarly, the LT and NLT molecular variants and their stage at diagnosis did not reach statistical significance (P=0.089), but the fact that both these factors i.e. delay in diagnosis and molecular variant adds to the tumor burden cannot be undermined as a whole because within the ERG the stage distribution among the LT and NLT was statistically significant (P=0.015) where LRG showed no obvious stage distribution within the other 2 molecular variants. Furthermore, only the tumor volume of Her-2 enriched variant in the NLT group showed statistical significance (P=0.036) with mildly positive correlation (Pearson=0.271) against the total delay, meanwhile the tumor volume of other molecular variants had no obvious trend against the total delay. This as a whole strengthens our point of view that when these individual factors are analyzed as a group, a definitive pattern can be highlighted that influences tumor burden in comparison to when viewed separately.

A number of different factors including age at diagnosis, tumor volume, lymph node infiltration, distant metastases, molecular subtype and grade at presentation have been used collaboratively to group patients into various risk categories such as the NIH consensus criteria[22], the Nottingham prognostic index[23] and the St Gallen criteria[24]. Breast carcinoma being a multi-factorial disease assessing the above factors in combination to one another is of greater clinical value than viewing them in isolation. On the contrary, implementation of these risk categories have shown better value when assessing prognosis in group of patients rather than individual patient with breast cancer in daily clinical practice, hence newer more advanced modalities such as molecular techniques including gene expression profiling consisting of hormone receptors ER, PR, Her-2, antibodies to CK5/6, Epidermal growth factor receptor, Ki67 expression have been used to quantify prognosis on individual basis.

Since breast cancer within the family enhances the chances of impacting the first degree relatives which was also supported in our study with 22.2% of the subjects having a positive family history of the disease hence we can look into BRCA gene as one of the screening modality which can help in detecting disease at a much earlier stage.

Our study had a few limitations, which include small sample size from a single breast cancer set up in Karachi, patients who had neo-adjuvant chemotherapy were disregarded in the study, any patient with a delay of more than two years was excluded due to human error in recalling dates and stage IV disease with metastasis was excluded hence it could be said that our results cannot be generalized to the entire population.

It is recommended that future researches should be conducted on a large scale that would cover more than one breast cancer set up, the studies should also correlate other immunologic markers such as Ki-67, CD44, CD24, BRCA, EGFR and ALDH1 to the prognosis of breast cancer and lastly, the studies should evaluate the response of hormonal therapy given post mastectomy in luminal and non-luminal types of breast cancers that can help in tailoring the drug regimens.

CONCLUSION:

Delay in diagnosis due to lack of screening modalities, lesser awareness among low socioeconomic groups and inaccessibility to tertiary care were not the major causes of aggressive tumors at diagnosis in developing countries, instead all the major known risk factors influence to the tumor burden collectively which includes molecular subtypes, grade at presentation and histological tumor variant.

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Review Article DOI: https://doi.org/10.51985/JBUMDC2019048

Peri-Implantitis – A Growing Complication of Dental Implant Prosthesis

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ABSTRACT

Contemporarily, dental implant is considered as the gold standard for managing complete or partially edentulous patients. Even though with meagre rates of failure, peri-implantitis is one complication that is worth deciphering. The prevalence of peri-implantitis is reportedly increasing with time so correct diagnosis is the most important factor for proper management of peri-implant disease. Regular evaluation and elimination of risk factors (history of periodontitis, poor oral hygiene, diabetes, smoking, alcohol consumption, genetic traits, absence of keratinized mucosa and implant surface) are effective precautions against peri implantitis. The management of peri-implant mucositis is also considered as an important preventive measure for the onset of peri- implantitis. In addition to aspects of osseointegration, type and structure of the implant surface are of importance. For the treatment of peri-implant disease multiple conservative and surgical methods are available. To minimize its detrimental effects, it is important to take a holistic view of the condition. Therefore, this review gives an overview on the prevalence, etiology, risk factors, prevention and treatment of peri-implantitis.

Keywords: Complication, Dental Implant, Inflammation

INTRODUCTION:

Dental implants have become a well-accepted therapy for the replacement of missing teeth in dentistry. Dental implants have relatively better survival rate (>10 years) as compared to other dental prosthesis.[1] Success rates of around 88% were reported after 15 years follow-up.[2] In the last decade, increasing number of evidence have been reported on the presence of peri-implant inflammations which is one of the most common complications that effects the soft and hard tissues surrounding an implant which can eventually cause the implant loss. Therefore, strategies for treatment and prevention of peri-implant disease should be included in the modern concept of rehabilitation in dentistry.

In a successful implant, there's a tight seal between peri-implant mucosa and trans-mucosal component of implant.[3] It is generally considered that during initial healing phase after implant installation, there is a loss of crestal bone of around 0.5 and 2 mm.[4] Any additional bone loss after initial healing phase suggests peri-implant disease.[5] According to a study conducted by Renvert et al; any bone loss greater than 2mm is indicative of peri-implantitis.[5] Clinically, peri-implantitis can be determined by peri-implant mucosal inflammation, which includes redness, bleeding on probing and exudation, along with a loss of the supporting tissues which shows increases in probing depths and progressive radiographic bone loss.[6] Multiple factors are involved in the evaluation of peri-implant health and disease which include bleeding on probing (BOP) and changes in crestal bone level with or without deepening of peri-implant pockets (PPD).[7]

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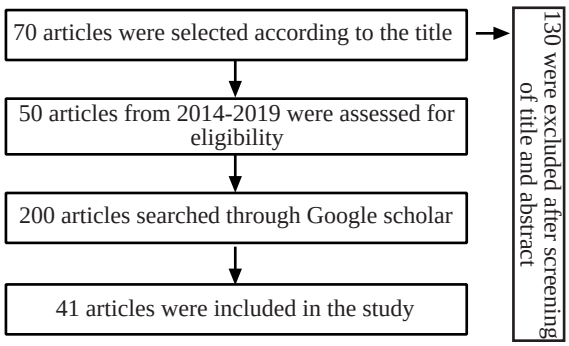
Received: 25-04-2019
Accepted: 01-10-2019

METHODOLOGY:

To obtain available data of interest GOOGLE and GOOGLE SCHOLAR were used as electronic databases. The literature search was performed on articles published from 2014 to 2018. Key words such as *Peri-implantitis, periimplant mucositis, definition of periimplantitis, risk factors, and treatment of perimplantitis* were used. Among 200 articles, 44 were short listed on the basis of suggested title. A major content of this article was based on risk factors and treatment options available for periimplantitis. Figure-1.

LITERATURE REVIEW:

DEFINITION AND DIAGNOSIS: In comparison with gingivitis and periodontitis which is affecting natural teeth, disease affecting soft and hard tissue surrounding implant is called peri-implant mucositis and peri-implantitis. Peri-implant mucositis is an inflammation of the soft tissues or



mucosa surrounding a dental implant, without additional bone loss after the initial bone remodeling that may occur during healing following the surgical placement of the implant.[8] Whereas 'Peri- implantitis is an inflammatory lesion of the mucosa surrounding an endosseous implant and with progressive loss of supporting peri-implant bone'.[3] It is thought that peri-implant mucositis usually leads to peri-implantitis if not treated on time.

ETIOLOGY AND PREVALENCE:

There are several reports on the prevalence of peri-implantitis which range from 1 to 47%. In a systematic review, the weighted mean prevalence of peri-implantitis was 22%.[9] Prevalence of peri-implantitis *was* evaluated, and revealed that 10% of all inserted implants and 20% of all implanted patients showed peri-implantitis.[13] Peri-implantitis results from an imbalance between the host response and oral biofilm at the implant surfaces. Formation of a bacterial biofilm around the implant is considered as a main etiological factor in the development of peri-implantitis.[10] Gram negative anaerobic bacteria found in bacterial biofilm includes Fusobacteria, Spirochetes, and black-pigmenting organisms such as Prevotella Intermedia.[11]

RISK FACTORS:

Correct diagnosis is the most important factor for proper management of peri-implant disease.[14] The risk factors which result in peri-implantitis include history of periodontitis, poor oral hygiene, diabetes, smoking, alcohol consumption, genetic traits, absence of keratinized mucosa and implant surface.[15]

Oral hygiene: Microbial colonization of the implant surface takes place as soon as it is exposed to the oral cavity.[16] Inaccessibility can interfere with oral hygiene maintenance which can cause peri-implantitis.[17] In a study, peri-implantitis was developed in 48% of the implants due to lack of proper oral hygiene maintenance because of inaccessibility.[18]

History of periodontitis: Periodontitis is one of the most common oral disease which is ranked as 6th most prevalent disorder in its severe form.[19] The worldwide prevalence of periodontal disease in the general adult population is 30-35%.[5] According to WHO estimates, the prevalence of chronic periodontitis estimates in the Pakistani population is 30%.[20] Whereas in a cross sectional study, the incidence of peri-implantitis was found to be 15.1% in the non-periodontitis and 26% in subjects with a history of periodontitis.[21] Roccuzzo et al. followed 149 patients and categorized them as periodontically healthy, moderately and severely compromised. He reported that the frequency of bone loss =3 mm (0%, 9.4%, 10.8%) and PD=6mm (4%, 16%, 24%, respectively) was increasing significantly with each group. The result also concluded that the peri-implantitis treatment was more extensive in patients with the history of periodontitis.[22] Donati et al. reported in a 20 year follow up study that the risk of peri-implantitis was more in the patients with the history of periodontitis.[23] So there is strong evidence that the history of periodontitis is a major risk factor in the development of peri-implantitis with different outcome of implant therapy in patients with or without periodontal disease.

Diabetes mellitus is a chronic metabolic disease which presented as hyperglycemia with other side effects. Diabetes as a relative contraindication for implant has always been controversial due to impaired healing found in diabetic patients.[24] Aguilar-Salvatierra reported that the peri-implantitis increased with patients having elevated level of HbA1c.[25] The cross-sectional study of 5 years conducted by Daubert Dm et al. showed an elevated risk for peri-implantitis of 1.9 in diabetics.[26] On contrary, the prospective study of Oates et al. reported no evidence of clinical signs of peri-implantitis 1 year after implantation.[27]

Smoking: Smoking causes impairment of various adaptive and innate host responses.[28] Several studies have affiliated smoking with dry socket, tooth loss, periodontitis and impaired wound healing post-surgery.[29] Another study evaluated that the smoking has a negative effect on implant survival.[30] The patients who smoke before the placement of implant were 35% more prone to implant failure and those who smoke after placement have 75% risk of failure as compared to non-smokers.[31,32] The relationship between peri-implantitis with smoking is still controversial, as some studies have failed to identify any significant differences of peri-implantitis among smokers and non-smokers.[33,34.35] Thus, the information available on the smoking as a risk factor to peri-implantitis is still insufficient.

Implant surface: In vivo studies showed no correlation between design and surface texture of the trans-mucosal portion of implants to peri-implantitis. The development of peri-implantitis is not effected by dimensions of keratinized tissues present between mucogingival junction and the peri-implant mucosal margin. Some evidence studies suggest that excess cement is also a risk factor for peri-implant imflammation.[12]

TREATMENT:

Surgical treatment is usually required to treat peri-implantitis whereas only nonsurgical therapy can be used to treat to peri-implant mucositis. It was particularly emphasized proper oral hygiene maintenance, diagnosis and professional plaque removal is required to prevent any implant related disease.[12] Adjunctive therapy (use of antiseptic mouthwashes/ antibiotics) showed no improvement in the efficacy of professionally administered plaque removal (PAPR) in peri implant disease patients.[36]

Non-Surgical Treatment: Peri-implantitis is not completely eliminated by mechanical debridement alone. Therefore, adjunctive therapies rather than mechanical debridement alone have been recommended, such as laser, antibiotics, and photodynamic therapy.[37] A randomized clinical trial

about peri-implant therapy showed that non-surgical mechanical therapy alone and with adjunctive use of Perisolv(chloramine based oral gel), are equally effective in treatment of peri-implantitis up to 3 months.[38] Another study showed Adjunctive therapy (use of antiseptic mouthwashes/antibiotics) showed no improvement in the efficacy of professionally administered plaque removal (PAPR) in peri implant disease patients.[36] Another study of peri-implant mucositis do not recommended adjunctive antiseptics/antibiotics (local and systemic) over alone. A study by Schwarz et al. recommended alternative measures for plaque removal (i.e. Glycine powder air polishing, erbium- doped, yttrium aluminium garnet laser—ERL) and adjunctive local antibiotics over the MD alone.[39] J Gordon et al, assessed the long-term clinical outcomes following non-surgical therapy of peri-implant diseases and concluded that both mechanical debridement with Chlorhexidine and ERL were successful on the long-term, but failed to attain a complete disease resolution.[40]

Surgical treatment: De Waal et al. suggest that "experience of the surgical team," "amount of bone loss" and "smoking" are the factors which indicate the prognosis of surgical treatment of peri-implantitis.[41] It is reported that at least 12 months follow up is required to evaluate the effects of surgical treatment but 6 months follow up can also be useful as patient enters maintenance phase by 6 months.[42]

Resective peri-implantitis surgery: Koldsland et al. conducted a study on short-term effects of surgical treatment of peri-implantitis, and its prognostic indicators. He indicated that the inflammation is reduced by resective peri-implantitis surgery but bleeding on probing/suppuration was still present which requires evaluation and long-term maintenance. The presence of suppuration and bone loss of more than 7mm prior to surgical treatment reduces the effects of treatment.[43]

Smoking has a negative prognostic effect on the surgical treatment of peri-implantitis.[41] Characteristics of implant surface also have an impact on the prognosis of surgical treatment of peri-implantitis.[44] Machined/smooth surfaces recorded to have less inflammation than the modified implant surface. However this variable was not recognized as a prognostic indicator in multilevel studies.[43] The location of implant also plays a part in outcome of the treatment. Lingual and buccal sites have less pocket depth and bop as compared to approximal sites. There are several possible reasons for this. First, buccal/lingual sites shows more mucosal recession. Secondly, alveolar bone of neighboring teeth have a higher level which might create a bony inclination towards the implant. In addition, the location of the implant site is also effected by accessibility of oral hygiene.[43]

CONCLUSION:

Peri-implantitis is a severe complication that results in failure of dental implants. Thus, proper oral hygiene along with concerned local and systemic factors should be kept in view to prevent the inflammation of the surrounding tissues of the implant. Various surgical and non-surgical treatment modalities are also available to counter peri-implantitis and should be applied as per their indications. Correct diagnosis of peri-implant disease is critical for appropriate management of peri-implant disease.

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Review Article DOI: https://doi.org/10.51985/JBUMDC2019139

Hydrocephalus and Its Diagnosis - A Review

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ABSTRACT

Hydrocephalus is enlargement of the ventricular system of the brain due to increased cerebrospinal fluid (CSF) volume and pressure. Congenital hydrocephalus is further classified as communicating and non-communicating depending on whether there is an obstruction to the flow of CSF or not.

Multiple causes have been identified in literature which has been summarized as an imbalance in the production and absorption of CSF. It can lead to cognitive impairment, cerebral palsy and visual field defects.

It is crucial to identify this condition prenatally as it can leave a debilitating impact on the fetus. Several modalities like ultrasound, computed tomography scans (CT) and magnetic resonance imaging (MRI) have been used to diagnose hydrocephalus. These can help reduce the disease burden and provide means for timely decisions.

Key words: Classification, Congenital Hydrocephalus, Diagnosis, Dilated Ventricles, Hydrocephalus, MRI, Prenatal, Ultrasound, Ventriculomegaly.

INTRODUCTION:

Hydrocephalus is the enlargement of the brain ventricular system due to an excess in the volume of cerebrospinal fluid (CSF). This excess of CSF maybe due to an overproduction or poor reabsorption, which results in raised intracranial pressure (ICP)[1]. Accumulation of CSF in the subarachnoid space is called *external hydrocephalus*. Multiple causes have been identified in literature which have been summarized as an imbalance in the production and absorption of CSF.[2,3,4] Ventriculomegaly is a general term used for dilatation of ventricular system of the brain, irrespective of the cause.

Enlarged ventricles were identified by Hippocrates, Galen and Arabian physicians. It was then thought that this condition developed due to *extracerebral* collection of water.[5] However, Thomas Willis in the 17th century clarified the concepts of the ventricular system and in the 18th century important anatomical structures like the Aqueduct of Sylvius, foramen of Monroe and foramen of Magendie were identified by Francis Sylvius, Alexander Monroe and Francois Magendie respectively.[2] In 1886 Key and Retzeus documented the present-day concept of the flow of CSF. In 1913 Dandy and Blackfen were able to categorize and distinguish between communicating and non-communicating types of hydrocephalus.

The first sterile method for drainage of CSF by ventricular puncture was developed by Wernicke. Followed later by serial punctures, eventually ventriculo-subarachnoid-subgaleal shunt was developed in 1893 by Mikulicz. These procedures were polished over the years and centuries and eventually the year 1950 led to the evolution of modern-day shunts.[2,5]

Cerebrospinal fluid is produced as an ultrafiltrate by the walls of the capillaries that are present in the choroid plexuses of the ventricles and is secreted by the action of Na^+/K^+ ATPase pump present in the walls of these capillaries.[4,6]

Recent data suggests that CSF plays an essential role in homeostasis and neuronal functions. Therefore, any disturbance in its flow can result in hydrocephalus and also dementia if this condition occurs in adults.[7,8]

Walter Dandy developed experimental models to investigate the pathophysiology and treatment modalities for hydrocephalus in 1919. Based on these models the author was the first one to classify hydrocephalus as communicating and non-communicating.[9,10]

Various researchers have classified hydrocephalus is different ways, Raimondi explained it as *"water head"* and hence included all the conditions which were responsible for increased volumes of intracranial water under the heading of hydrocephalus. The author, therefore, not just included the actual etiologies responsible for causing hydrocephalus but also linked it to various conditions which were responsible for this vascular edema.[11]

Mori et al attempted to classify hydrocephalus based on the impact of treatment by studying 1450 patients in Japan.[12]

Oi and Di Rocco classified hydrocephalus in relation to the mechanism of obstruction to flow as primary, due to impedance to flow at a single point which included Arnold Chiari malformation and secondary hydrocephalus due to abnormal growth or hemorrhage.[13]

In a review article by Shakeri et al., hydrocephalus was classified based on the pressure of CSF as (i) normal pressure

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Received: 26-11-2019
Accepted: 31-12-2019

hydrocephalus, (ii) high-pressure hydrocephalus (iii) hydrocephalus due to aqueduct stenosis with a frequency of 47%, 27% and 15% respectively.[4]

Liu J and Rekate classified hydrocephalus into communicating, due to insufficient absorption of CSF in the subarachnoid space and obstructive or Non-communicating hydrocephalus due to a blockade in the flow of CSF from the ventricles to subarachnoid space. Obstructive type is further sub-categorized into a congenital and an acquired type.[14,9]

Kalyvas et al. describes congenital hydrocephalus as occurring in infancy and does not have any associated cause. However, when there is a known specific causative factor such as an invasive tumorous mass or an injury or insult to the brain, acquired hydrocephalus may occur.[15,16]

Tully in 2014 attempted to classify hydrocephalus in a simplified way which has been summarized in table 1.[3]

Etiology:

Hydrocephalus presents a wide and comprehensive etiology which ranges from idiopathic, to structural defects to chromosomal anomalies. This wide array of etiology has been summarized in table 2 [3,15,17,18,19,20,21,22,23]

Maternal Risk factors are, diabetes, hypertension (pre-existing, gestational, pre-eclampsia and eclampsia), diabetes mellitus, gestational diabetes, pregnancy induced obesity, drugs (antidepressants, proton pump inhibitors (PPIs), nitrosatable drugs, metronidazole), maternal alcohol and illicit drug use and congenital infections[19,24].

METHODOLOGY:

Data Base Used: Google scholar, Pub- Med, Pak Medinet and ERIC.

Articles filter criteria: the used keywords generated about 100 articles ranging over a period of 20 years, the search was then tweaked and words like prenatal, dilated ventricle and ventriculomegaly were added. This resulted in reducing the number to about 70 articles. Out of these the articles ranging from 2010-2018 were selected. The abstracts and methodology of these articles were first read and eventually after going through the complete article they were finally selected. However, 2 articles from the years 1995 and 1999 were also included because of their relevance to the topic under review.

DISCUSSION:

Incidence of congenital hydrocephalus was found to be maximum in Africa, followed by Latin America and lowest

Table 1: Classification of hydrocephalus

S. No.	Type of Hydrocephalus	Distinguishing Features
1	Acquired	Occurs as result of an extrinsic cause e.g. hemorrhage, infection, mass/ tumor etc.
	Congenital	Present at birth and is due to an intrinsic cause e.g. obstruction of aqueduct of sylvius
2	Obstructive / non-communicating	Obstruction of CSF pathway
	Communicating	No apparent source of obstruction identified
3	Syndromic	Hydrocephalus is present in association with other main physical characteristics
	Non-syndromic	Phenotype consists of findings only in the brain

Table 2: Etiology of Hydrocephalus

S. No	Type of Hydrocephalus	Etiology
1	Acquired	Hemorrhage, neoplasm, bacterial meningitis, cytomegalovirus, enterovirus, toxoplasmosis, prenatal intraventricular hemorrhage, drugs like misoprostol, metronidazole, antidepressants, isotretinoin
2	Obstructive / non-communicating	Aqueduct stenosis due to intrauterine hemorrhage or infections, obstructive intracranial cysts,
3	Communicating	Excessive CSF production, poor CSF reabsorption due to hemorrhage,
4	Syndromic	L1cell adhesion molecule associated, Fried syndrome, Walker-Warburg/Muscle -Eye-Brain disease
5	Non-syndromic	Occurs with other brain lesions like holoprosencephaly, rhombencephalosynapsis, agenesis of corpus callosum, lissencephaly

Table 3: Classification of ventriculomegaly on prenatal ultrasound based on atrial measurements

Ventriculomegaly	Atrial diameter
Mild	10 -12 mm
Moderate	12.1-15 mm
Severe	>15mm

Table 4: Use of prenatal ultrasound in detection of hydrocephalus and other congenital anomalies

Title of study	Author	Journal & Year of publication	Method	Results
Correlation between prenatal diagnosis by ultrasound and fetal autopsy findings in second-trimester abortions[21]	Hauerberg et al	Acta obstetricia et gynecologica Scandinavica, 2012	52 pregnant females were included, ultrasound scans done between11-13 weeks and 18-22 weeks. Results were correlated with autopsy findings	Full agreement b/w ultrasound &autopsy findings in 46% fetuses, in 90% main US findings were confirmed.
Comparison between prenatal ultrasound and postmortem findings sin fetuses and infants with developmental anomalies[31]	Vogt et al	Ultrasound in Obstetrics & Gynecology. 2012	Retrospective review of 455 autopsies of fetuses and infants with congenital anomalies was conducted and compared with prenatal ultrasound performed by trained midwives and obstetricians	84% of prenatal ultrasound findings correlated with that of autopsy findings and statistically significant p values were obtained for 98% cases with main diagnosis.
Concordance between prenatal ultrasound and autopsy findings in a tertiary care center[38]	Rodrigues et al	Prenatal diagnosis. 2014	Retrospectively evaluated 151 elective termination of pregnancy and the findings were compared with ultrasound findings done between 11-13 weeks and 20-22 weeks	91.5% central nervous system, 91.3% renal system and 90.2% cardiovascular system anomalies were confirmed at autopsies, however, less correlation was found in musculoskeletal and abdominal anomalies.
Prenatal diagnosis of fetal ventriculomeg-aly: agreement between fetal brain ultrasonography and MR imaging.[39]	Perlman et al	American Journal of Neuroradiology. 2014	Prospective study in 162 fetuses, mean gestational age was 32 weeks, ultrasound was performed in axial plane and MRI was performed in coronal plane	Cut off for ventriculomegaly was kept at 10mm, the k-score was 0.94 for the narrow ventricle and 0.84 for wide ventricle. These results were in perfect harmony thereby establishing the concordance between the two modalities
Accuracy of prenatal diagnosis of isolated aqueductal stenosis.[36]	Emery et al	Prenatal diagnosis. 2015	Retrospective study, stenosis of aqueduct of Sylvius was detected prenatally in fetuses with ventriculome-galy by ultrasound and MRI and compared with findings on postnatal MRI and CT scans	All 6 cases of isolated Aqueductal stenosis and 6 cases of aqueductal stenosis with associated anomalies were accurately identified and confirmed by postnatal MRI and CT scans
Neurological outcome in fetuses with mild and moderate ventriculomegaly[40]	Tonni et al	Revista Brasileira de Ginecologia e Obstetrícia. 2016	62 fetuses diagnosed as mild and moderate hydrocep-halus on prenatal ultrasound and results were compared with fetal and postnatal MRI	Bilateral ventriculomegaly was identified in 58% of fetuses and this finding was later supplemented and supported by MRI findings in 85% of cases.

in USA, 316, 145 and 68 per 100,000 births. A prevalence of 0.34/1000 births was noted in Nigeria.[25] Male predilection was also observed by Dewan et al in their metanalysis study.[26,27] Another author observed a relationship between male gender and the development of intracranial hemorrhage which is a risk factor for developing fetal hydrocephalus.[19]

Age specific metanalysis study conducted by Isaac et al reported highest prevalence of 88/100,000 in pediatric age group followed by 11/100,000 in adults; and 175/ 100,000 in the elderly.[28] Munch et al in their study found a prevalence of 1.1/1000 live births out of which 75% had a positive family history.29 A very high prevalence of 4 -12/ 10000 live births was observed in China as compared to European countries. The authors also observed a decline in congenital hydrocephalus because of widespread use of folic acid as part of antenatal care[30] Both studies found a higher prevalence of hydrocephalus in low income countries as compared to high income countries.[31,32]

Liu J, in 2018 reported the prevalence rates of 4.65 per 10,000 (European regions), 11 per 10,000 (Denmark) 5.9 per 10,000 births (California) and 7 per 10,000 births (China).[14] An incidence of 1 in 10,000 live birth is reported in Pakistan by Salat et al.[33]

Ninety nine percent women undergo prenatal ultrasound scans as part of normal routine during pregnancy. With advances in technology, the enhancement of experience and skills of sonologists the accuracy with which ultrasound scan can detect prenatal anomalies has increased over the decade.[31,32] Ultrasound scans have proven to be a safe, useful, easiest and most sensitive test for the diagnosis of hydrocephalus.[34] Addario et al., identified the sensitivity of ultrasound to diagnose ventricular enlargement as 93.5 %, especially if scans are done at 24 weeks of gestation or later. Sensitivity of the scans drop to 35% if done before 24 weeks of gestation. This difference in sensitivity, as stated by Addario et al., is most likely due to the course of disease itself rather than any errors of measurement.[35]

The size of lateral ventricle should be measured as part of routine screening done in second trimester. Scans done in axial plane maximize the visualizations of frontal horns, septum pellucidum and the atria of the lateral ventricles.[34] The part of lateral ventricle where the body, posterior horn and inferior horn meet is called the atrium of the lateral ventricle.[17] Between 15 – 40 weeks of gestation the atrial width remains constant, that is < 10mm. Any increase in this measurement leads to ventriculomegaly which is classified by atrial width measured on ultrasound.[17,34,36,37] Details of these measurements are described in table 3

Several researchers have compared the results of prenatal ultrasound with MRI and postnatal autopsy results which have been summarized in table 4.

Hydrocephalus has been known to be associated with several other congenital anomalies which can be easily detected on prenatal ultrasound. Study conducted by Mahmoud et al in Sudan found stenosis of aqueduct of Sylvius to be most commonly and frequently associated anomalies (45%) followed by spina bifida (30%), Arnold Chiari malformation (20%) and Dandy Walker formation (5%).[41] Ventricular septal defect, tetralogy of Fallot, diaphragmatic hernia, gastroschisis, hydronephrosis, urinary malformation are a few others which have been found to be associated with hydrocephalus.[31,32]

Literature has identified shunt systems and endoscopic 3rd ventriculostomy as treatment modalities for hydrocephalus.[2] Recurrence risk of hydrocephalus was found to be 55.6% in same sex twin, 6.6% in first degree relative, 2.1 % in second degree relatives and 1.7% in third degree relatives.[28,42]

Impact of untreated hydrocephalus depends on the severity of the hydrocephalus. It can lead to cognitive impairment, cerebral palsy and visual field defects.[28,42,43] Abnormal neurodevelopment is associated with mild to moderate hydrocephalus in 7 -8 % fetuses whereas with severe hydrocephalus in 58% fetuses.[36]

CONCLUSION:

Ventriculomegaly or hydrocephalus can easily be identified in second trimester by transabdominal scans since it can lead to a multitude of neurodevelopmental disorders. Therefore, its early detection and screening is advised. CT scans can diagnose hydrocephalus and other anomalies as efficiently as ultrasound however it has risk of exposing the fetus and mother to radiations. Above all, this modality has high cost and lack of availability concerns attached to it in a developing nation such as ours. MRI is another significant tool to diagnose hydrocephalus, a coherence was identified in both modalities' ultrasound and MRI, thereby enhancing the counselling and the pre and post-natal management of the patients.

Ultrasound remains as one of the cheapest, cost effective, easily accessible and most sensitive modalities which can prove to be of great value in detecting hydrocephalus. This in turn can allow the physicians and parents to make timely decisions regarding rehabilitation or termination of pregnancy thereby reducing the disease burden in the society.

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Review Article DOI: https://doi.org/10.51985/JBUMDC2019127

Anatomy and Clinical Significance of Sacral Hiatus

Samia Khalid Khokhar, Aisha Qamar

ABSTRACT

The sacral hiatus is a gap on the dorsal surface of the sacrum formed by the non-fusion of the lamina of the fourth and fifth sacral vertebrae. A multitude of anatomical alternations of hiatus have been reported involving metric and non-metric parameters. These have been identified during radiological investigations, surgical procedures or discovered in anatomical and anthropological research studies. For successful outcomes in the clinical setting, it is vital that awareness of identified and newly discovered anatomical variations is achieved through review of literature. Objective of this article is to provide a systematic review of the reported anatomical variations of sacral hiatus with its clinical significance.

Key words: Anatomical variations, Clinical relevance, Sacral hiatus.

INTRODUCTION:

The sacral hiatus is a gap in the midline on the dorsal surface of the sacrum. It is formed by the non-union of the lamina of the fifth and less frequently fourth sacral vertebrae. On either side of this gap, the inferior articular processes of the fifth sacral vertebra extend downwards to form the sacral cornua[1]. The cornua are an important landmarkfor identification of the area of sacral hiatus. On gross examination the gap of the hiatus is usually shaped like a triangle, having an apex above and base below. The level of the apex may lie as high as the second sacral vertebraor as low as the fourth sacral vertebra. The base may be present at the coccyx, fifth or second sacral vertebra. An apex at the fourth sacral vertebra level is considered normal[2].

Dry human sacral and radiological studies have revealed that the hiatus shapes range from triangular, U, inverted V, dumbbell, M to irregular[3-5]. Complete absence of hiatus has also been observed in 1.2% cases in African population[6] and 2.22% in Indian population[3]. On the surface the hiatus is usually marked two inches above the tip of the coccyx beneath the natal cleftwith sacral cornua on each side. It is used to access the sacral nerves, coccygeal nerves and filum terminale present in the sacral canal for management of pain, administration of anesthetics, and endoscopy[7-10].

Uses of sacral hiatus in thecaloscopy, trans-sacral endoscopy, myelography, minimally invasive spinal surgery and hernia repair have also been documented. It has been observed that for successful and complication free procedures, variations of sacral hiatus are to be taken into deliberation[11-13]. Symptoms of low back pain and urinary incontinence have also been associated with variations of sacral hiatus. Low back pain has been attributed to congenital absence of dorsal wall of sacrumwhich gives attachment to the extensor muscles of the spine. A decrease in the surface area for attachment of muscles of the back causes low back pain with minimal muscle spasm[14-17].

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Received: 05-11-2019
Accepted: 31-12-2019

METHODOLOGY:

A comprehensive search was undertaken using Google, Google Scholar, PubMed, Medline and Pakmedinet. Articles were selected from the years of 2009-2019 using keywords and phrases such as sacral hiatus anatomy, anatomical variations of sacral hiatus, clinical relevance, radiography, and morphometry. Articles irrelevant to the topic, outdated text and those written in foreign language were excluded. Total of 50 articles were selected and 45 were used for writing this review.

Review of Literature:

Anatomy

The sacrum has been considered as the keystone of the human body because it forms a link between the spine and hip bones. Its name has been derived from the Greek language meaning ‘temple’ or ‘holy bone’. It was regarded as “sacred” by the ancient Egyptians and believed to be necessary for resurrection[19].

Anatomically, the sacrum is described as a “triangular” bone with a base, apex and ala (wing). The base is formed by the upper surface of the first sacral vertebra at the level of the sacroiliac joint. The base forms an angle of thirty degrees or more as it slopes downwards and forwards. It then curves down over the pelvic cavity. Considering the shape, the apex is formed as the base tapers off. The ala are formed by the fusion of the costal elements and transverse processes. They are present lateral to the body of the first sacral vertebra and are crossed from medial to lateral by the sympathetic trunk, lumbosacral trunk and the obturator nerve. The sacrum also has a concave, smooth pelvic surface, an auricular surface on lateral side for articulation with the ilium and a convex, rough, irregular dorsal surface. The pelvic surface has four

ridges which are formed by the fusion of the bodies of the sacral vertebrae and represent the intervertebral discs. The sacral foramina are also present on the sides. These foramina transmit first to fourth sacral nerves. On the sides of the anterior sacral foramina is the lateral mass. It is related to the rami of anterior sacral nerves and gives attachment to the piriformis muscle. The dorsal surface is closed in the midline by the fusion of the laminae of the sacral vertebrae to the sacral crests. The fusion of the laminae, however, is not complete in the lower end leaving a gap through which the filum terminale passes to attach to the coccyx. A canal is formed in the midline of the sacrum that contains the meninges and posterior root ganglia of the sacral nerves. This is called the sacral canal and the gap inferior to it the sacral hiatus[2].

The sacral hiatus is normally closed by fibrous tissue that forms the superficial sacrococcygeal ligament. On either side, it has the sacral cornua, which are an extension of inferior processes of the fifth sacral vertebra. These cornua are used to mark the area of the hiatus. The hiatus is also related to the area of attachment of intermediate layer of muscles of the back. These include the erector spinae muscle formed by the iliocostalis, longissimus and spinalis, gluteus maximus, and multifidus[20].

Morphometric Differences:

Dry human sacral studies have revealed that variations in the shape, length, diameter and position of the sacral hiatus occur in different races and genders alike. Normally described as being triangular, the hiatus is stated to consist of an apex and a base. However, a variety of shapes have been documented. These include the inverted 'U', inverted 'V', M, dumbbell, bifid and irregular[4,20,21]. Total absence of the sacral hiatus has also been reported in cases of congenital malformations of the vertebra such as spina bifida occulta. In Pakistan the overall incidence of congenital malformations of sacrum was found to be 34.5%. The prevalence of incomplete and complete spina bifida was 5.5% and 4.5% respectively[22].

Metric and non-metric analyses have been used in multiple morphometric studies involving the sacrum and sacral hiatus. Measurements of length, and antero-posterior and transverse diameters have been included in metric whereas levels of apex and base with reference to sacral vertebrae in non-metric assessment tools. Measurements were made by digital calipers in millimeters. Landmarks for measurements of length, transverse and antero-posterior diameters were distance between the apex and the base of the hiatus, the sacral cornua and from anterior to posterior walls of the sacral canal[5,23].

The length of the sacral hiatus has been linked to complications in procedures involving entry into the sacral canal[24,25]. It has been found that the longer length of the sacral hiatus is directly related to increase in the incidence of dural puncture. Since the normal level of dural sac termination is at second sacral vertebra, a hiatus with long length has decrease in the distance between the apex of the hiatus and dural sac[26,27]. Measurements conducted in morphometric and radiographic studies have shown that length of sacral hiatus varies. Measured distances ranged from 28.7±7.1mm[13], 20.6+ 8.8mm[17], 18.88± 7.58mm[21], 32.9 ±9.9mm[28], and 11-30mm (mean distance25.2mm)[29].

Anteroposterior diameter from the apex is significant when access to the sacral canal is required. A variety of observations related to geographic locations have been documented. In the Indian population 0.48cm and 0.5cm have been found[17,21], Arabs 0.53cm[29], 0.5cm in White Americans and 0.6cm in African Americans[30], 4.46cm in Turkish population[28] and 4.6 + 2mm to 6.1 + 2.1mm in Japanese population[10]. Furthermore, it was found that the diameter decreases with advancing age. A diameter of less than 3.7mm was observed to cause difficulty in caudal epidural anesthesia[10]. The intercornual distance reported in various studies is also variable. An average of 19.5mm in Arab[13], 17.47+3.23mm[17] in Turkish, 17 mm in Americans[30], 4.88mm in Indian[31], and 10.2+ 0.35mm was reported in Japanese population[32].

Features which can be observed on gross examination of the bone either in radiographs or dry sacra are the non-metric parameters. These include the shape, and level of the apex and the base with reference to the sacral vertebrae[13].

Shape of the hiatus is one of the most important landmarks. Higher level of apex is not to be considered safe because of proximity to the termination of dura mater[13]. The most common shape observed has been the inverted 'U' as documented by Kumar et al (41.5%)[3,] Bagheri (33.33%)[13], Aggarwal (70.8%)[21] and Nadeem (56%)[29].

An apex level at S4 has been a consistent finding in multiple studies[3,13,21,32]. Incidence of apex at S4 ranges from 60-68%. Similar findings found in multiple studies indicating apex level at S4was observed in70.11% of Arab [13],68.42% as well as 76.23% Indian[17,21] and 65% of Japanese[32]populations. Apex at other levels was also found including 1% at S1[32], 62% at S3[29], and 11.49% at S5[13]. The level of apex is used to decide the length of the needle to be used in interventional procedures. In majority of studies, it has been found at the level of S4 with incidence of 60-68%[13,17,21,32]. These findings are in agreement with another study which observed apex at level of S4 in 65-68% of the sacral vertebra[10]. Base of the sacral hiatus has been frequently observed to lie at S5[17,21,29].

Clinical Significance:

Caudal epidural anesthesia/analgesia

It involves injection of anesthetic through the sacral hiatus to access the epidural space. It can be used for management of chronic pain, surgical anesthesia and analgesia in children and adults. Thorough knowledge of sacral hiatus anatomy

helps to improve the success rate of this technique[10]. It can also be used in orthopedic practice and obstetrics[11,32]. Identification of apex and antero-posterior diameter of sacral hiatus is crucial for successful procedure. Safe option for access is through the base of the hiatus[21,28]. Anatomic abnormalities may cause failure of caudal epidural block in 3-11% patients[32]. Sacral hiatus approach was also used in anorectal surgeries for regional anesthesia. It was found that success rates of caudal epidural anesthesia increases with experience of the surgeon and that it has significant results in pain reduction[33, 34].

Thecaloscopy

It is a minimally invasive procedure used to access the subarachnoid space. A flexible endoscope is used to access the thecal space. Sacral hiatus can be used for trans-sacral endoscopy. Dimensions of sacral hiatus width (transverse diameter), lumbosacral angle and level of termination of dural sac are necessary for complication free procedure[35,36].

Myelography, Treatment of Urinary Incontinence and Urological Calculi

Sacral hiatus can also be used as a potential route for stimulation of sacral nerves in the treatment of urinary incontinence in post-operative patients especially after radical prostatectomy. A study observed significant difference in response rates of sacral nerve stimulation totally by sacral hiatus when compared to alternate route via sacral foramina. Route involving sacral hiatus had 60% positive response rate whereas alternate route had 20% response rate[37].

Mechanical low back pain

Low back pain may be associated with a decrease in surface area for the attachment of the extensor muscles of the back on the dorsal wall of the sacrum[16]. In a study it was found that the dorsal wall of sacra was deficient in 40% male as compared to 27.2% females. According to the study, 7.5% of cases had no sacral hiatus[17]. High percentage of low back pain was associated with variable deficient wall in the referred articles [16, 17].

Congenital Anomalies

Anomalies related to sacrum include spina bifida. In Pakistan overall incidence was 34.5%. Prevalence of incomplete spina bifida was 5.5% and complete defect was 4.5%. Symptoms of backache, urinary and neurological symptoms were prevalent in such cases[22].

Methods of Studying the Hiatus

Radiological

X-ray of lumbosacral spine, pelvis or sacrum has been used for studying the sacrum and hiatus. More advanced techniques such as CT scan and MRI have been used for detailed imaging via three dimensional views[38]. Ultrasound has also been used for determination of optimal angle of needle insertion for caudal epidural anesthesia and comparison between male and female patients with low back pain[39-41].

Anthropometric

Majority of the studies used dry human sacra for morphometric, and comparison studies. These studies assessed the differences observed in male and female sacra with their clinical significance, anatomical variations related to locations, racial variations and related congenital anomalies[42-45].

CONCLUSION:

The sacral hiatus is a gateway to access the sacral and coccygeal nerves. It has significant potential as an alternate route in surgical, palliative and interventional procedures. Variations related to the length of the hiatus have potential clinical implications and require further investigations.

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Case Report DOI: https://doi.org/10.51985/JBUMDC2019128

Intravenous Lipid Emulsion Therapy In Paediatric Poisoning

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ABSTRACT:

Lipid emulsions are traditionally used as a part of total or partial parenteral nutrition. However in the past few years role of lipid emulsions has been identified in the management of poisoning and overdose caused by the lipophilic agents. Although most of the evidence comes from the various case reports. We are reporting 2 cases of poisoning in the paediatric age group. In both the cases multiple poisoning agents were involved with tricyclic antidepressants being the common agent in either case. Lipid emulsion therapy was used as an adjunct in addition to the traditional poisoning management. Both the girls recovered completely without any neurological deficit. The sequence of events observed provides a considerable evidence regarding the role of ILE therapy in the successful management of both the cases. However more research is required in the area to develop definitive guidelines regarding the use of Intravenous lipid emulsions in paediatric poisoning caused by lipophilic agents.

Keywords: Lipid emulsion therapy, Paediatric poisoning, Tricyclic antidepressants poisoning.

INTRODUCTION:

Lipid emulsions are originally used as a part of total or partial parenteral nutrition in patients unable to take orally. However role of lipid emulsions in the treatment of poisoning has been observed in last few years in animal models as well as in humans[1]. In 2006 first case report proving the role of intravenous lipid emulsion therapy as a treatment option for acute drug poisoning was published[2]. After that various other cases and subjective reports also supports the role of intravenous lipid emulsions in the treatment of toxicity caused by various drugs and pesticides[3,4,5].

Intravenous lipid emulsion is an accepted therapy for the treatment of severe cardiac toxic effects caused by local anesthetics and is being studied as therapy for hemodynamically unstable patients poisoned with several lipophilic medications like TCAs, calcium channel blockers, barbiturates[6].

Here we report two cases: A 6 year old female, case of accidental poisoning and an 11 year old female, a case of suicidal poisoning. Multiple drugs were involved in either case with tricyclic antidepressant being a common drug. In both the cases lipid emulsion therapy was also used in addition to the recommended management of poisoning with specific agents.

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Received: 29-11-2019
Accepted: 12-12-2019

CASE STUDY:

CASE 1: A 6 years old female was brought to Pediatric ER at 9.30 am when her mother found her unconscious with frothing at her mouth.

On examination the child was unconscious with GCS of 4/15(E1M2V1), tachycardia with heart rate of 130/minute, shallow breathing, constricted and nonreactive pupils, oxygen saturation of 78% in room air and RBS was 53mg/dl. ECG showed sinus tachycardia with no other abnormality. ABGs showed uncompensated metabolic acidosis. The urine toxicology report was positive for opiate and tricyclic antidepressants.

Naloxone at 0.1mg/kg was given, after a single dose of naloxone the GCS improved to 9/15(E4M3V2) and the pupils were now bilaterally equally reactive to light.

Sodium bicarbonate infusion was started as a part of traditional management of TCA poisoning treatment protocol so as to maintain alkaline PH. No further improvement was noted for next 2 hours in the GCS and patient was still having tachycardia, so it was decided to start intravenous lipid emulsion therapy. As no pediatric dosage has yet been recommended we followed the adult dosage regimen for ILE therapy. Initially 2 boluses were given at 1.5ml/kg, each over 3 minutes and 5 minutes apart. Still no improvement was noted so lipid emulsion infusion was started. It was continued for next 6 hours. ABGS showed improvement gradually as well as the patient regained GCS of 13/15(E4M5V4) and the tachycardia improved after 2 hours of starting ILE infusion. Patient was clinically and hemodynamically stable in the next 12 hours. Serum amylase and serum triglycerides levels were found to be normal after the therapy.

During her ICU stay she did not develop any hemodynamic instability or seizure disorder.

CASE 2: An 11 years old girl was bought with complaint of unconsciousness for past 5 hours.

Examination revealed that she had a GCS 4/15 (E1V1M2), with mid dilated, sluggishly reactive pupils. her pulse rate was 90/min, respiratory rate of 30breaths/min, BP was 115/60. Her planters were bilateral up going but deep tendon reflexes were normal. ECG was normal. ABGs showed metabolic acidosis and urine toxicology was positive for benzodiazepines, barbiturates and tricyclic antidepressants.

The patient was given flumazenil as an antidote for benzodiazepine poisoning. It was given in 3 divided doses with a gap of 1 minute along with GCS monitoring. GCS improved to 8/15(E2M4V2).Sodium bicarbonate infusion was maintained. Lipid emulsion therapy was given initially as 2 boluses at 1.5ml/kg over 3 minutes and 5 minutes apart. The GCS of the patient improved to 12/15(E4M5V3) after the second bolus. The lipid infusion was continued for next 6 hours. ABG showed improvement and were completely normal in next 3 hours after starting infusion. The patient regained full GCS of 15/15 with down going planters which were initially up going after 4 hours of starting infusion. Serum amylase and triglyceride levels were monitored after the therapy, no abnormality was observed. Psychiatric consult was done which revealed that the child has pressures for performing well in studies from the family, which lead to the suicide attempt. She was advised psychotherapy and she improved on follow-up.

More than 1 kind of drug was involved in both the poisoning cases with TCA being the common agent. In both the cases amount of the drug ingested is unknown. We observed that the use of lipid emulsion therapy hastened the recovery in either case with no major side effects.

DISCUSSION:

Lipid emulsion therapy is well known for the purpose of total and partial parenteral nutrition. Its role has also been proved in the treatment of cardiac toxicity caused by local anesthetics. There is an emerging role of lipid emulsion in the management of acute poisoning as well; although the data available is based mainly on the case reports.

According to the scientific literature how lipid emulsion works in management of poisoning is not fully understood. However, there are various mechanisms by which the lipid emulsion is believed to be beneficial in the management of poisoning. Two most likely possibilities are:

1. Intravenous lipids act as a 'lipid sink'. Lipophilic agents are easily absorbed by or easily attached to lipids but are not absorbed by water. The practical effect of this characteristic is that a highly lipid-soluble drug or chemical will not remain in the intravascular compartment but will pass through cell membranes and reach binding sites in the tissues. A bolus of intravenous lipid may provide an intravascular lipid sink that attracts and absorbs highly lipid-soluble drugs or chemicals before they reach the tissues, or the lipid will actively pull drugs or chemicals from tissue binding sites[7].

2. The second possibility involves fatty acid metabolism. Under normal circumstances, the myocardium uses fatty acids for energy. Local anesthetics inhibit fatty acid metabolism in the heart, and experiments in animals have indicated that intravenous lipid may reverse the cardiac toxic effects caused by high doses of bupivacaine by providing an exogenous energy source for the myocardium. This mechanism supports the already accepted theory of the role

Table 1: Comparison of the two cases.

	CASE 1	CASE 2
AGE , WEIGHT	6years, 18 kg	11 years, 35 kg
DRUGS	TCA, Opioids	TCA, Benzodiazepines, Barbiturates
DOSE	Unknown	Unknown
TIME OF PRESENTATION AFTER POISONING	More than 12 hours	Around 8 hours
TOXICITY ONSET	Loss of consciousness(GCS 4/15), metabolic acidosis, tachycardia, shallow breathing	Loss of consciousness(GCS 4/15), metabolic acidosis
TREATMENT	Naloxone at 0.1mg/ kg, Sodium bicarbonate infusion, Intravenous lipid emulsion therapy at 1.5ml/ kg as 2 boluses 5 minutes apart and then an infusion for 6 hours at 0.25 ml/kg/min.	Inj Flumazenil 1 mg in 3 divided doses. Sodium Bicarbonate infusion, Intravenous lipid emulsion therapy at 1.5ml/ kg as 2 boluses 5 minutes apart and then an infusion for 6 hours at 0.25 ml/kg/min.
TOXICITY REVERSAL (Time of onset)	GCS improved to 13/15, improvement in ABGS noted after 2 hours of starting lipid infusion.	GCS improved to 12/15 after the second bolus, metabolic acidosis resolved completely in 3 hours of starting infusion. GCS 15/15 after 4 hours of infusion.

of lipid emulsion in reversal of severe cardiac toxic effects of local anesthetic[8].

ACMT guidelines suggest the following dose for lipid resuscitation therapy:

Dose of lipid emulsion is 1.5ml/kg bolus given over 2-3 min, it can be repeated after 5 min to a maximum of 3ml/kg.For the purpose of continuous infusion dose is 0.25ml/kg/min till the patient becomes hemodynamically stable preferably through a central line[9].

Most of the published case reports on the subject describe adults, only a few cases regarding children and adolescents have been reported. The first pediatric case report published in 2011 where ILE therapy was used in case of acute poisoning. It reported a 20 month old girl who ingested a large amount of TCA and presented with seizures and hemodynamic instability. She did not respond to the traditional poisoning management protocol; Intravenous lipid emulsion therapy was administered, which resulted in successful recovery of the patient[10].

An article published in 2013 reviewed all the case reports published regarding the use of ILE therapy in children and adolescents. It concluded that almost all the cases showed a beneficial effect of ILE therapy with side effects observed only in 1 case report. The dosage regimens were not well defined though[11].

TCA is lipophilic drug, and when taken in excessive amounts it has cardiovascular and central nervous system side effects. In both our cases, mainly neurotoxicity was noted. Lipid emulsion therapy was used and it demonstrated rapid recovery in both the cases. Although due to multi agent poisoning and multiple therapies given, it is impossible to attribute the success in saving lives exclusively to Lipid Emulsion therapy; however the sequence of events observed in toxicity reversal proves a substantial role of ILE in the favorable outcome observed in both the above cases.

Lipid emulsion therapy is a promising therapy and a cheaper option in the cases of acute poisoning with lipophilic agents where a specific antidote is not available for the chemical[12]. Jeffrey Brent a renowned medical toxicologist, gave a remarkable statement in this regard in an editorial published few years back "It is fair to say that based on what we known so far, no patient dying of cardio toxic drug poisoning should do so without a trial of lipid rescue"[4,13]. We can suggest that the statement is well-thought-out in terms of lipid rescue for neurotoxic effects of lipophilic drugs as well; at least in both our cases. More research is required into the subject and proper guidelines need to be developed for pediatric usage.

CONCLUSION:

This is the first ever reported use of successful intravascular Lipid Emulsion therapy in the management of life threatening effects of poisoning with multiple agents, with TCA being the common agent in both the cases in a Public Sector Pediatric Tertiary Care setting in Pakistan. This case report add to the increasing evidence of the role of Lipid emulsion therapy in the treatment of acute poisoning with lipophilic agents and also proves pediatric safety profile.

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Commentary DOI: https://doi.org/10.51985/JBUMDC2019136

Pre-Pregnancy Obesity: A friend or foe for Vitamin D

Fareeha Shahid, Farhan Muhammad Qureshi

INTRODUCTION:

Vitamin D and its active metabolite 1,25 - dihydrooxyvitamin D (1,25(OH) 2D) has been generally recognized as repertoire of many classical (calcium balance and bone metabolism) and non-classical effects (non-calcium actions) such as promotion of insulin secretion and its action, immunomodulation. Absorption of calcium and phosphorus depends on sufficient vitamin D levels. Its low level leads to demineralization of bone both in children and adults. Vitamin D has also a significant role and has potential to influence many factors in the developing fetus. Newborns are at high risk of developing hypocalcaemic tetany as a consequence of maternal deficiency of vitamin D.

Pregnancy, Obesity and Vitamin D:

Insufficiency of Vitamin D is an emerging public health concern across the globe especially among the women during their reproductive phases of life. Obesity in the reproductive phase of women's life is another notable risk factor for vitamin D insufficiency that increases the risk of maternal and fetal complications.[1] The time after conceiving is crucial for women as they are more susceptible to vitamin D deficiency, as they sustain their own vitamin D reservoirs along with their babies.[2] Moreover, More than 14 million women suffer from maternal complication every year, especially in developing countries.[3]

Maternal vitamin D levels directly linked to the fetal vitamin D levels and its insufficient level is a major cause of low gestational fetal weight, neonatal hypocalcaemia, reduced weight and size infant and juvenile rickets.[4,5] Prepregnancy obesity related adverse outcomes such as miscarriage, preeclampsia and gestational diabetes and its associated fetal overgrowth are mediated by the deficiency of active metabolite of vitamin D which has a significant role in the development and function of placenta, inflammation, angiogenesis, immunomodulation and insulin sensitivity.[2] The development and right progression of fetus and placenta depends on vitamin D receptors and an activating enzyme (1-a-hydroxylase) in placenta which acts as a modulators. They also plays a significant role in maternal as well as fetal blood glucose regulation.[6] The excess of adipose tissue in overweight and obese individuals causes sequestering of active form of vitamin D and stored it, in an inactive form in the body.[7] Thus and so, it has been noticed among pregnant women whose body mass index (BMI) >30 are at major risk of vitamin D insufficiency due to decrease insulin sensitivity.[8,9] Studies suggest that healthy, non-obese individuals had higher levels of circulating active metabolite of vitamin D as compare to the obese individuals.[10] Dark skin individuals and inadequate exposure to sunlight due to any reason is associated with reduction in the synthesis of cholecalciferol (D_3) in skin through UV radiation from sunlight that is considered to be the significant source of vitamin D.[11] It might be the reason of vitamin D deficiency among obese individuals including obese pregnant women as they spend most of their time at home and not exposing themselves to sun.[12] Hence, pregnant woman who is vitamin deficient both due to sunlight exposure and due to insulin sensitivity must concerned their own health as well as their babies. Obese and women with dark pigmented skin or covered skin need to be careful regarding their vitamin D levels and consult to the health practitioner to rule out the cause and treatment if required.

Public Health Concern:

Being the public health issue, pregnancy related metabolic disorders and deregulations becoming challenge not only for the mother and its baby but also influence and burdened the entire family. Efficient and effective strategic interventions such as public awareness and professional educational programs at mass level regarding benefits of sun exposure at prescribed phase, physical activities, healthy and nutritional diet work as a helping hand and ultimately reduce the overall economic, social, emotional and health related burden.[13] In addition, family counselling also play a vital role to deal with the lethal scenario and to prevent the prenatal, intranatal and post natal life threatening conditions in mothers and adverse health consequences in the newborns.[14] Despite the recommendation in many documents of National Health Service guidance regarding the prevention and management of Prepregnancy condition such as obesity and diabetes but, unfortunately, there is limited provision so far for such service. Health promotion techniques helps to gain insight to improve general health and able to persuade them to adopt healthy lifestyle. Further, weight loss guidance prior to conceive the child would help to control the pregnancy related problems and able to cope the possible complications. Screening for the vitamin D status in child bearing age especially among the obese women who are planning to

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Received: 16-12-2019
Accepted: 22-12-2019

conceive may benefit by giving high dose supplementation to improve their vitamin D reservoirs as well as their babies.[15]

Recommendations to combat vitamin D deficiency:

Despite a dearth evidence that supports the vitamin D supplementation and treatment in clinical trial settings, it is widely accepted that regular intake of vitamin D supplements and treatment of its deficiency is safe and recommended for all women especially the pregnant and lactating mothers. However, consultation with doctor is necessary for the optimal dose of vitamin D use to achieve potential health benefits in short and long term. All pregnant and breastfeeding women should also be encouraged to receive adequate, healthy and nutritious food. Fortification of food with vitamin D may improve the deficiency and overall health status, not only in women but also in children. World Health Organization (WHO) recommended vitamin D supplementation in pregnant women in its 2012 guidelines. Sunlight is the most important source of vitamin D, hence sunlight exposure at a prescribed phase is necessary for pregnant women as well as general population. However, the time and amount of sunlight exposure is not known and rely on many factors such as time of the day, amount of skin exposed, latitude and season, skin pigmentation (lighter skin pigments synthesize more vitamin D as compare to darker pigments) and use of sun shades and screens.

CONCLUSION:

Obesity especially prepregnancy obesity has been identified among multiple factors involve in vitamin D deficiency among women especially pregnant women. Steps must be taken to identify and treat the condition both in clinical and public health setting in order to combat the complication arise in mother, fetus and in newborn. The emerging cases of obesity before and during pregnancy rises the maternal, fetal and newborn vitamin D deficiency related complication will threat to become a serious public health issue, if not planned and managed efficiently and effectively.

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DOI: https://doi.org/10.51985/JBUMDC2019131

Ergonomic Awareness: Simple Solution To Prevent Work-Related Musculoskeletal Disorders (WMSDs)

Khalid Aziz, Ambreen Shehzad, Syeda Tahniyat Ali

Musculoskeletal disorders are injuries or dysfunctions that affects muscles, bones, nerves, tendons, ligaments, joints, cartilages, and spinal discs. They include sprains, strains, tears, soreness, pain, carpal tunnel syndrome, hernias, and connective tissue injuries of the structures previously mentioned[1]. Musculoskeletal disorders is a major source of disability and loss of work time among employees[2]. During the last two decades, there is an increase use of Visual Display Units (VDU) in majority of occupation which leads to various work-related musculoskeletal disorders. Musculoskeletal symptoms of VDU users are believed to have a multi-factorial etiology including repetitive motion, excessive force, prolong sitting or standing, workplace ergonomics, excessive physical loads and psychosocial factors[3].

Most common examples of WMSDs are low back pain, neck pain, carpal tunnel syndrome, tendinitis, epicondilitis etc[4]. Musculoskeletal Disorders affect large numbers of people across most industries and occupations, have the potential to lead to long and serious disability, and impose heavy costs on employers and on society[2]. In order to prevent MSDs a simple ergonomic awareness and approach can reduce the risks and disability among workers in any workplace. According to the International Ergonomics Association (IEA) Council an official definition of the discipline of ergonomics "is the scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data and methods to design in order to optimize human well-being and overall system performance"[2].

To solve all these problems simple strategies can be applied by an organization to enhance their employee's productivity. Re-designing work-stations and use of adjustable furniture are frequently advised[5]. On the other hand, proper posture awareness among workers who are involved in any occupation that demands prolonged static postures especially in front of computers or any visual display units can be carefully trained to differentiate between good and bad postures. Taking regular stretch breaks from sustained positions, monitoring frequency of physical loads, stress management are some of the simplest solutions to adopt by any organization or workplace for the betterment of their workers or employees.

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Received:10-12-2019
Accepted: 20-12-2019

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Peer Reviewed Multidisciplinary Quarterly Published Journal
ISSN (print): 2220-7562, ISSN (online): 2617-9482
Recognized by PM&DC (IP/0072)
Online edition is available at URL: https://jbumdc.bahria.edu.pk,
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