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Covid-19 and the Fear of Stigmatization

Quratulain Javaid

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There are some medical conditions, which make the patients extremely hesitant in contacting the physicians. When the patients are fearful of going to physicians, it is essential to determine whose responsibility it is.[1] These days, everyone is fearful of the impact of COVID-19 or corona virus. The disease was started in China and within the time span of few months it crossed the boundaries of China. This public health emergency has affected almost all parts of the globe with its devastating influence. Not only the developing countries but also the developed nations of the world are stunned by the distressing illness that has become a puzzle that is yet to be solved.[2]

There are various physical as well as psychological aspects associated with this dangerous viral disease. As the physical component of the disease is significant, likewise the psychological aspect has its vitality. One of the psychological characteristics of the COVID-19 is stigmatization. The terminology of stigmatization refers to acts in which prejudice and discrimination are faced by the patients for certain characteristics. These features become the identity of the individuals and therefore lead to social avoidance by the affected individuals. It is not only limited to a single person but also can include their families and the communities they belong to. In the infectious disease outbreak occurrences, like COVID-19, stigmatization becomes a public problem.[3] The history of medical illness beholds many instances when the patients having infectious diseases witnessed stigmatization. The situation at present has not changed at all. Such patients witness variable derogatory manifestations ranging from denial of health care, provision of care that is not up to the health standards, verbal abuse etc. In times of communicable outbreaks, there remains a tug of war between the confidentiality of the patients' medical information and the public disclosure of patients' details.[4] When the COVID-19 initially appeared in China, it was given a discriminatory name 'Chinese virus'.[5] This sort of stigmatization is not novel. In 2014, during the EBOLA outbreak, the Africans were stigmatized and so was the case when the SARS outbreak ensued; the East Asians were at the target.[6]

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The effects of being stigmatized for an associated illness like COVID-19 are far detrimental than the illness itself. When the patients' personal information like names, area of residence, work place etc. are known to the general public, it causes anxiety, resentment, depression and mental stress. Over and above that, the trust that exists between the physician and the patient eventually becomes lost. Those with the symptoms are then hesitant to report to the hospitals and disclose about their detailed medical histories. As a consequence of this mistrust in the health professionals, issues like community based prejudice, social seclusion and violation of confidentiality arise. There is likelihood that due to absence of disease reporting, the illness would spread more. This is because of the fact that when there is reluctance in contacting the health professionals, provision and the facilities of care are not reached to the effected ones.[7]

Media reports across the globe have documented several stories of discrimination against the ones who are positive for COVID-19. The sufferers' dwellings are pigeonholed. On the entrance, one can see written, 'the home is under Quarantine, do not visit'. Besides, those affected by virus are stamped on their hands so when they go in public every one could know they are suffering from the disease.[8]

Health and government officials have to make sure that the confidential information of the COVID-19 positive patients should not be leaked. Only that amount of evidence should be made public that is necessary for the containment of virus without providing harm to the integrity of the patients. In instances when revelation of the information outweighs confidentiality of the patient (for example when tracing of the persons who came in contact with patient could not be tracked then it is necessary to make the public disclosure). In such circumstances, it is essential to consider the following. The first and foremost, the harmful outcomes of disclosure to the patient in the form of loss of job, tenancy etc. The detrimental effects of disclosure to the patient and the public in seeking medical advice in future with the development of mistrust in the health professionals. The possible benefits of disclosure to the public.[9]

In our country, the positive patients are also battling this enormous distress and trauma. On the one hand, they are fearful of their physical health and on the other hand, the individuals are scared of their leaked identities. They have the insecurity that they and their families would be denounced and treated in a different way. Those living as tenants are terrified of being asked to leave the place of stay. Loss of

job is also an issue which remains a threat for such vulnerable persons. The fears of being treated as different and being bullied due to the contagious illness are enough for them not to report to the health facilities. These reasons are source of mistrust in the health sector among the individuals.[10]

The panic and fear in the surrounding environment necessitates that cognizance of the facts related to the disease must be known to the public. A message should be communicated to all that COVID-19 is a disease like other diseases and those having the disease are similar to others and not at all inferior to others. This can be achieved by employing use of radio, news channels, newspapers, social media (Facebook, twitter and WhatsApp) etc. We need to teach public that the patients suffering from corona virus should not be blamed. There should be sessions on psychological reassurance. There is a need for the authorities to provide free of cost helpline numbers to assure consultation with the health professionals that could eradicate the uncertainties and apprehensions. Consequently, spread of falsehoods and the associated threat of stigmatization can be nipped in the bud.

Author Contribution:
Quratulain Javaid: 1. Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data
2. Drafting the article or revising it critically for important intellectual content
3. Final approval of the version to be published
4. Agreement to be accountable for all aspects of work in ensuring that questions related to accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Original Article

Role of Rifaximin in Prevention of Recurrent Hepatic Encephalopathy in Chronic Liver Disease

Sahar Farzand, Abdul Latif Khattak, Rafi ud Din, Karamat Hussain Shah Bukhari, Muhammad Shahbaz Amin, Shahzeb Ahmed Satti

ABSTRACT

Objectives: To determine the efficacy (in terms of recurrence) of rifaximin in Hepatic Encephalopathy (HE) in chronic liver disease.

Study Design and Setting: A descriptive study carried out from 4th September 2018 to 3rd March 2019 at the department of Medicine, Combined Military Hospital, Quetta.

Methodology: A total of 104 patients of chronic liver disease with HE, 25-65 years and both genders were included. Patients with gastrointestinal hemorrhage, chronic renal insufficiency and anemia were excluded. Then tab Rifaximin 550 mg twice daily along with standard prescription i.e. Lactulose 30 to 60 ml in two to three divided doses per day was given to each patient and efficacy was noted**.** Statistical analysis was carried out using SPSS version 20.0. Age, duration of disease and Conn's score was presented as mean and standard deviation. A p value = 0.05 was considered as significant

Results: Age range in our study was from 25 to 65 years with a mean of 45.73 ± 8.13 years. Most of the patients 54 (51.92%) were between 46 to 65 years of age range. Out of the 104 patients, 77 (74.04%) were male and male to female ratio was 2.9:1. Mean duration of disease was 13.66 ± 3.77 months. Mean conn's score was 4.77 ± 1.43. Efficacy (no recurrence) of rifaximin in HE in chronic liver disease was found in 85 (81.73%) patients.

Conclusion: It was inferred that rifaximin is useful in decreasing the recurrence of HE in chronic liver disease patients with previous episode/s of encephalopathy.

Keywords: End stage liver disease, Hepatic encephalopathy, Rifaximin

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INTRODUCTION:

Hepatic Encephalopathy (HE) is one of the most challenging complications of advanced liver disease. It can be defined as "a neuropsychiatric syndrome caused by porto-systemic venous shunting, ranging from minimal to overt HE or coma". HE occurs in as many as about 30%–45% of patients with cirrhosis while corresponding figure for patients who have undergone TIPS (transjugular intrahepatic porto-systemic shunt) is 10-50%. Minimal HE which is only detected with psychometric analysis is seen in approximately 20%–60% of patients with cirrhosis.[1]

Therapies for HE mainly aim at reducing the nitrogen load in the gut, as it is hypothesized that increased concentration of ammonia is the major abnormality, in patients with abnormal liver functional tests (LFTs) and porto-systemic shunting.[2] Lactulose, a non-absorbable synthetic disaccharide, by bacterial action results in acidification of colonic contents which facilitates the formation of non-absorbable NH_4 ion from NH_3. It also alters bowel flora so that fewer ammonia-forming organisms are present.[3] Non-absorbable disaccharides have been proved to be effective both in management and prevention of HE with a mortality benefit as compared to placebo.[4] Although lactulose seems to work in the acute setting, for durability of remission, different antibiotics have to be used. Several agents have been used for this purpose but rifaximin is by far the most

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frequently used antibiotic treatment for this indication i.e. prevention of recurrent HE.

As mentioned earlier; lactulose and rifaximin are the most commonly used agents for prevention of recurrent HE. However, compliance to lactulose is often limited due to adverse effects.[5] For this same reason, rifaximin is rapidly evolving as a therapy of first choice to decrease the incidence of recurrent HE. Rifaximin, a rifamycin derivative, is an oral antibiotic having a broad spectrum of activity and low risk of bacterial resistance which is absorbed through the intestinal mucosa in negligible amounts.[6] In different studies rate of recurrence of HE with Riafaximin treatment has been reported from 22.1% to 36.5%.[7] A Spanish study by Morillas et al[8] also showed that Rifaximin was effective in preventing and improving quality of life in patients with cironic liver disease. A recent meta analysis by Hudson and Schuchmann showed that adding rifaximin to lactulose was more effective in long term treatment of HE than lactulose alone[9]. Multiple treatment agents/strategies have been studied for treatment of HE , some (e.g. branched chain amino acids[10], L-ornithine L -aspartate[11], nutritional therapy[12]) were found to have some benefit while others (e.g. Acetyl L –Carnitine[13], Flumezanil[14], probiotics)[15] did not show any significant benefit, or the studies were inconclusive. These agents, therefore, have lost interest of clinicians, and are not being used routinely in clinical practice.

Above mentioned studies are from western researchers and have wide variations in results. This study was carried out to find out if Rifaximin has the same efficacy in preventing recurrence of HE in Pakistani population because it is an established fact that there is a difference of dietary habits and living styles as well as genetic makeup between Pakistani and western populations. While there are several studies[16,17] assessing role of rifaximin in treating HE, there are only a few[7] which have assessed its role in preventing HE recurrence. More data in this regard will provide better evidence to choose this medicine for this purpose or otherwise in Pakistani population.

METHODOLOGY:

It was a descriptive study for which Institutional review board of CMH Quetta issued a certificate for the study vide number CMH QTA-IRB 018.

All patients of chronic liver disease with history of at least one episode of HE (as per-operational definition). Duration of disease was >6 months. Child Pugh Class of A, B & C (these were not the source of bias as they were stratified in the final analysis). Patients 25-65 years of age and both gender were included in the study.

Exclusion criteria were patients with known hypersensitivity to rifamixin or excipients used in its formulation. Patients with psychiatric disorders (since diagnosing HE may be difficult due to comorbidity) which remain uncontrolled

For this study we defined hepatic encephalopathy as "new onset of overt neuropsychiatric abnormality/ies in a patient with pre-existing chronic liver disease'. Patients were labeled as having HE only when there was no competing pathology present to explain neuropsychiatric abnormality. Minimal (covert) hepatic encephalopathy, therefore, was not actively looked for and was not included in the study.

Total number of 104 patients of chronic liver disease with HE (as per operational definition) meeting the inclusion criteria were enrolled. Sample size of 104 cases had been calculated with 95% confidence level, 8% margin of error and assuming a recurrence rate of rifaximin in hepatic encephalopathy in chronic liver disease at 22.1%. Patients were given details of the study and an informed consent was obtained for enrollment. After taking informed written consent, Child-Pugh class was calculated. Tab Rifaximin 550 mg twice daily along with standard prescription i.e. Lactulose 30 to 60 ml in two to three divided doses per day was given to each patient and recurrence of hepatic encephalopathy was noted over a mean duration of 13.66 ± 3.77 months. All data was recorded on a specially designed proforma.

Statistical analysis was carried out using SPSS version 20.0. Age, duration of disease and Conn's score was presented as mean and standard deviation. Gender, child pugh class (A/B/C) and efficacy (yes/no) was presented as frequency and percentage.

Different possible confounding variables like age, gender, duration of disease and Child Pugh Class (A/B/C) were controlled by stratifying patients according to the values obtained. Post-stratification chi square was used to calculate their impact on efficacy. P value < 0.05 was considered as statisticially significant.

RESULTS:

Age range of patients in our study was from 25 to 65 years with a mean of 45.73 ± 8.13 years. Most of the patients 54 (51.92%) were between 46 to 65 years of age.

Out of the 104 patients, 77 (74.04%) were male with male to female ratio being 2.9:1 (Figure II). Mean duration of disease was 13.66 ± 3.77 months. Mean Conn's score was 4.77 ± 1.43. There were no drop outs or deaths during the period of this study. Distribution of patients with other confounding variables is shown in Table I.

Rifaximin was found to be effective (no recurrence) in HE in chronic liver disease was found in 85 (81.73%) patients. There was no significant difference between different age groups and genders (Table II). Table II also shows efficacy of Rifaximin with respect to duration of

disease and Child Pugh Class respectively.

DISCUSSION:

In this study the overall recurrence rate on Rifaximin was 18.2%. This is in keeping with the corresponding rate in study which reported a recurrence rate of 22.1% with rifaximin.[18] In another study by Ali et al, rate of recurrence of HE was 36.51%.[7] This minor difference may possibly be due to a smaller number of patients in study by Ali et al which enrolled only 63 patients in treatment group. However this can be further evaluated by enrolling a larger number of patients in future studies.

After oral administration, intestinal absorption of Rifaximin is negligible and the drug is concentrated in the lumen of the intestine. It has a reasonably wide-spectrum and has been shown to have in vitro activity against gram-positive as well as gram-negative aerobic and anaerobic intestinal bacteria. It has very low risk of generating bacterial resistance.[18] Randomized controlled studies have shown that rifaximin was more effective than non-absorbable disaccharides and was as effective as or more effective than other antibiotic drugs used in the treatment of acute HE.[19]

The study of Sanyal et al[20] concluded that patients taking a combination of lactulose and rifaximin had higher scores on health related quality of life questionnaires (HRQL). This is in keeping with efficacy of this combination for prevention of recurrent HE as in the same study the authors found that a deterioration in HRQL scores was associated with episodes of HE. We can therefore infer that by reducing the recurrence of HE, rifaximin improves quality of life of CLD patients.

Table I: Stratification of patients with different confounding variables (n=104)

Confounding variables		Frequency %age
Duration of CLD (months)	=12	32 (30.77)
	>12	72 (69.23)
Child Pugh Class	A	28 (26.92)
	B	57 (54.81)
	C	19 (18.27)

Table II: Efficacy of Rifaximin according to different variables

		Efficacy		P-value*
		Yes	No	
Age (years)	25-45	41	09	0.945
	46-65	44	10	
Gender	Male	65	12	0.231
	Female	20	07	
Duration of CLD (Months)	=12	29	03	0.118
	>12	56	16	
Child Pugh Class	A	23	05	0.588
	B	48	09	
	C	14	05	

*chi-Square

Rifaximin was used in addition to lactulose in this study patients, which is the most commonly combination used to treat acute HE and is also recommended in patients who have recurrence of HE on non absorbable disaccharides alone. The debate whether to use rifaximin either instead of or in addition to lactulose has persisted in spite of current practice guidelines which recommend lactulose as first-line treatment. In study by Morillas RM[8,] Rifaximin was effective when compared to placebo in 299 patients with history of recurrent encephalopathy (HE) in remission. Rifaximin 550 mg twice daily decreased the risk of recurrent episode of HE as well as the risk of hospitalization from HE. It is worth noting that more than 90% of patients in each arm of this study were taking lactulose at baseline. When further studied, it was revealed that patients who did not use lactulose at baseline did not have significantly different outcomes with rifaximin compared to placebo. Overall, treatment with rifaximin was well tolerated with positive outcomes[21]. We therefore did not include a Rifaximin only arm in our study.

Each successive episode of overt HE may leave increasing residual deficits in working memory, response inhibition as well as learning when patients are assessed by psychometric testing[22]. Standard treatment for an acute episode of HE includes non-absorbable antibiotics (such as rifaximin), lactulose or lactitol and correction of any precipitating factor. Patients with minimal (covert) HE need psychometric analysis for diagnosis which were not included in our study. We did not carry out detailed cognitive evaluation to diagnose minimal HE and this remains a topic for research. As mentioned earlier successive episodes of HE inflict progressive incremental loss of cognitive functions but in order to be diagnosed with confidence, such a loss will need repeated psychometric testing. It can thus be questioned if patients taking rifaximin any difference as regards cognitive function when compared to those who do not receive such treatment. Further research can address this very question looking at the loss of cognitive functions in patients with liver cirrhosis and making comparison between patients taking rifaximin and those who do not take any treatment.

Limitations of this study include a relatively smaller number of patients, and the fact that we did not stratify the response of treatment according to various precipitating factors for hepatic encephalopathy. It might be possible that rifaximin is more effective for one or more particular triggers of hepatic encephalopathy than others. Therefore it is recommended that any future researchers enroll larger number of participants and

stratify their results according to the different triggers identified. Future researchers may also look into cognitive functions of patients on and off treatment over a period of time.

CONCLUSION:

Results of this study showed that rifaximin is an effective agent for reducing the recurrence of HE in chronic liver disease patients. However, due to small size of our study, further research enrolling larger number of patients with randomization will provide further evidence for or against this statement.

Authors Contribution:
Sahar Farzand: Conception, Design, Data Collection & Analysis
Abdul Latif Khattak: Conception & Design
Rafi ud Din: Data Collection & Analysis, Drafting
Karamat Hussain Shah Bukhari: Final Approval
Muhammad Shahbaz Amin: Drafting
Shahzeb Ahmed Satti: Data Collection & Analysis

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Original Article

Comparison of Varying Bolus Doses of Oxytocin in Patients Undergoing Caesarean Spinal Delivery

Muhammad Salman Maqbool, Ayesha, Huda Shafqat

ABSTRACT:

Objective: To determine the lowest effective bolus dose of oxytocin to produce adequate uterine tone during elective caesarean delivery avoiding side effects.

Study design and setting: A study was conducted at Rawal General and Dental Hospital, from 10th Oct, 2018 to 27th May, 2019.

Methodology: Patients undergoing elective cesarean spinal delivery were randomly divided by computer generated numbers(n=155) into 5 groups A, B, C, D and E receiving 0.5, 1, 3, 5 and 10 units of injection oxytocin as bolus respectively after delivery of baby. Uterine contraction was assessed by gynecologist by manual palpation of uterus on a linear scale. Value of 8 was considered adequate and $\leq$ 8 inadequate uterine tone respectively. Heart rate, non-invasive blood pressure and oxygen saturation were noted before and after oxytocin bolus. All patients received oxytocin infusion. The primary outcome measure was the assessment of uterine tone at 2 minute of oxytocin bolus. The secondary outcome variables included shortness of breath, chest discomfort, top-up bolus administered, hemodynamic variables, epigastric discomfort and oxytocin related effects (tachycardia, epigastric discomfort and hypotension).

Results: The use of 5 units oxytocin (group-D) showed most optimal uterine contractions, 61.3% in comparison to commonly used 10 units bolus dose (group-E) 48.4% with minimal side effects like, less tachycardia(12.9% versus 72.9%) and hypotension (12.9% versus 32.3%), no top-up bolus dose was required in 54.8% cases and no complain of epigastric discomfort was observed.

Conclusion: Low doses of oxytocin are effective in terms of uterine contraction with minimal side effects.

Keywords: Caesarean section, Maternal hemodynamics, Oxytocin, Phenylephrine, Uterine atony.

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INTRODUCTION:

Caesarean section rate in developed countries varies from 20-25%.[1] Uterine atony has been stated as the main cause of obstetric hemorrhage in up to 30% in patients undergoing cesarean delivery.[2]Uterotonics are drugs that initiate and maintain adequate uterine contractility after placental delivery thereby helpful in reducing blood loss from the site of placental attachment and decreases incidence of post-partum hemorrhage by up to 40% .[3] Oxytocin is the most common uterotonic drug used in caesarean deliveries.[4] Just after delivery of baby a bolus of oxytocin is given that is usually followed by infusion. In addition to its beneficial effects, its side effects include tachycardia, hypotension, epigastric discomfort, headache, flushing and chest pain.[5]

Tachycardia and increased cardiac output are considered to be a reflex response to hypotension, however it may have a deleterious effect in patients with compromised cardiac status.[6] Oxytocin has a weak anti-diuretic effect which is associated with fluid retention and pulmonary edema.[7]

In United Kingdom the use of oxytocin bolus is a standard treatment although doses vary from 5 to 10 units[8] (IU) as bolus that is usually followed by slow intravenous (IV) infusion, though top-up bolus may be required.[9] There is paucity of literature regarding effective dose of oxytocin particularly in developing countries. Recent studies have proven effectiveness of low dose oxytocin bolus ranging from 1 to 3 units.[10] Even cardiovascular collapse and death has been reported following rapid administration and high dose of oxytocin.[11]

Phenylephrine is alpha adrenergic receptor agonist and is vasopressor of choice to prevent and treat post-spinal hypotension during cesarean section. A dose of 100µg is commonly used and it results in increased blood pressure

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along with reflex decrease in heart rate thus it may prove effective for prevention of hypotension and tachycardia associated with oxytocin use. [12]Mohta M, et al. pointed in study that prophylactic phenylephrine 100 µg showed no change in systolic, diastolic and mean arterial pressure in initial 3 minutes following oxytocin use, whereas other group in study receiving saline showed significant fall in mean and diastolic blood pressure though heart rate showed little change in both groups for same time period of observation.[13]Significant variability occurs among health care physicians (obstetrician and anesthetist) as regard uterotonic agent administration in parturient undergoing cesarean section as stated by Orbach-Zinger S and colleagues[14] in their study, highlighting the importance of developing national guidelines for oxytocin use which will reduce use of high bolus dose and increase patient safety. In a randomized controlled study done, at Maula Baksh Teaching Hospital, Sargodha, 2 units oxytocin was compared with 5 units oxytocin in patients undergoing cesarean section, they concluded that 2 units oxytocin causes significantly less tachycardia (32% versus 61.33%) and hypotension (4% versus 17.33%) as compared to 5 units oxytocin.[15]Primary purpose of the study was to evaluate and compare adequacy of uterine tone assessed by attending obstetrician (by manual palpation of uterus) at two minutes of receiving varying bolus dose of oxytocin in parturient undergoing cesarean spinal delivery rated on linear scale of 1-10(1 being minimum and 10 being maximum). A value of 8 and $\leq$ 8 was taken as adequate and inadequate uterine tone respectively. The study rationale is the need of time to have a base for using lower bolus doses of oxytocin (clinically effective) rather than commonly used higher dose which have adverse effects as stated. Uterine atony can result in severe post-partum hemorrhage, gravid hysterectomy and maternal morbidity. The study algorithm was designed to cover inadequate uterine tone (uterine atony) with 'rescue' bolus of two units of oxytocin and repeated once if needed. Further uterine atony was addressed by adding oxytocin to ongoing infusion. It was hypothesized that 5 unit is better than commonly used 10 units of oxytocin with fewer side effects. Keeping in view above considerations, this study was aimed to compare and evaluate clinical effects of differing oxytocin bolus in patients undergoing cesarean spinal delivery.

METHODOLOGY:

A study was conducted at Rawal General and Dental Hospital, Islamabad from 10th Oct,2018 to 27th May, 2019. The approval of study was obtained from Institutional Dean and Head Research Ethics Committee, Rawal Institute of Health Sciences issued letter No. RIHS-REC/032/18. Total 155 patients (31 in each group) were enrolled in this study. All patients were planned for elective caesarean delivery with a Pfannensteil incision, placed in American Society of Anesthesiologists (ASA) physical status class 1-3.[16] Subjects were randomly divided into five groups by using computer generated numbers. Pre-anesthesia evaluation and informed written consent was taken in all cases. Excluded cases were allergic to oxytocin, known risk factors for post-partum hemorrhage (including abnormal placentation, history of uterine atony), inherited or acquired coagulation disorder, preeclampsia, HELLP syndrome, fixed cardiac output state e.g. aortic stenosis, shock. In operation theatre after placing two 18G intravenous lines, baseline vitals (non-invasive blood pressure, heart rate and oxygen saturation) were noted. All patients received a crystalloid fluid as "co-load"[17] of 500 ml ringer lactate. Spinal anesthesia was managed by team of two consultant anesthesiologists with more than eight years post-fellowship experience using injection bupivacaine spinal 0.5% hyperbaric (12 mg) in sub-arachnoid space over a period of 10 seconds and placed supine afterwards. The sensory and motor block was evaluated by pin prick in mid-line and modified bromage scale by Breen TW, Shapiro T and colleagues[18] at 3 and 8 minutes. Vitals (pulse and blood pressure) were noted before and after spinal anesthesia. Block was assessed till fourth thoracic sensory level achievement before surgery began. Also noted was hypotension, tachycardia, vasopressor or atropine need, epigastric discomfort and APGAR score.[19] Hypotension was defined as a decrease in mean blood pressure =20% of the baseline value (or < 90mmHg)[20] and each episode of hypotension was treated with intra-venous bolus of 50-100 µg phenylephrine.[12,13] Increased sympathetic drive in noted in parturient and tachycardia was defined as a maternal heart rate =120 beats / min.[20] After delivery of baby; group A, B, C, D and E patients were given 0.5,1,3,5 and 10 units of injection oxytocin as bolus respectively given by consultant anesthesiologist using hidden tagged syringe provided by fellow consultant anesthesiologist and both were part of study team with fixed roles. All patients also received oxytocin infusion of 30 units after bolus injection. Vitals were also noted before and after oxytocin bolus at 1,2,3,6 and 9 minutes interval. Uterine contraction was assessed by attending obstetrician not part of study (with at least four-year experience in obstetrics and were blinded to dose of oxytocin) two min after bolus oxytocin by manual palpation of uterus. In case of inadequate uterine contraction (score of $\leq$ 8) 'rescue' top- up of oxytocin in aliquot of 2 units was given and repeated once if needed. In case of persistent inadequate uterine tone there-after 10 units of oxytocin were added to on-going infusion. The primary study outcome measure was the assessment of either adequate or inadequate uterine tone at 2 minutes after administration of the initial oxytocin bolus dose. Any episode of secondary outcome variables e.g., shortness of breath, chest discomfort, arrhythmia, hypotension, flushing or epigastric discomfort along with side-effects associated with oxytocin (tachycardia, hypotension, epigastric discomfort) were noted. The hematocrit/ hemoglobin values were measured a day before planned procedure and 24 hours after surgery, as intra-operative blood loss estimation, as done by Anya SU and

colleagues[21] in their study. Secondly (blood loss is often dispersed and mixed with amniotic fluid) in cesarean section is poorly reproducible and also typically an under estimate whereas comparison of surgical blood loss from one institution to another or from one obstetrician to another is a problematic task, adequacy of uterine contraction by using oxytocin helps in reducing blood loss.[22] Also noted were rescue doses of oxytocin. Sample size was calculated using World Health Organization calculator and with statistical assumptions taking confidence interval of 95% and alpha error of 5% (authenticated complication of nausea and vomiting in 2 units group syntocinon = 5% and complication of nausea and vomiting in 5units group syntocinon = 32.5% respectively). The sample size was calculated to be 31 cases in each group (A-E).[23] SPSS analysis was done with version 16. P-value <0.05 was considered as statistically significant.

RESULTS:

The mean age of study population was 28+/- 4.7 years with range from 16-41 years. The mean hemoglobin pre-operatively and post-operatively of all cases in study (n=155) being 11.2 and 10.8 gm/dl respectively, while similar period mean hematocrit values were 34.2% and 32.8% respectively. Prophylactic atropine was used in 2 cases (1.3 %), after sympathetic block atropine was given in 66 cases (42.6%), both pre- and intra-operatively atropine was administered in 3 cases (1.9%) and no atropine was needed in 84 cases (54.2%) of patients in the study. After spinal anesthesia in 48 cases (30.96 %) of study population hypotension was observed treated by injection phenylephrine 100µg bolus.[12,13] while in 107 cases (69 %) no hypotension was noted. The mean APGAR Score[19] was 7.73(SD of .92) at time of delivery of baby and 9.56(SD of .98) at an interval of 5 minutes (this variation in score was due to intra-uterine death of 2 babies). The mean pulse rate /minute following sympathetic block in study was 101.49(SD of 33.85). The mean systolic and diastolic blood pressure (in mm Hg) following spinal anesthesia being 116.33(SD of 19.79) and 67.67(SD of 16.03) respectively. As we analyzed the data, the frequency of adequate uterine contraction was highest in group D(5 units bolus) however statistically there was no significant difference among all groups(p value=0.314).When we compared group B(1-unit bolus) with least observed adequate uterine contraction, with group D(5 units bolus) the best uterine contraction, a P-value of 0.04 shows that the difference between group B and D was statistically significant. Since in routine practice and as per mentioned in text books a 10 units bolus of oxytocin is stated so we have compared our results between the group D(5 units) and group E(10 units)[24]. In comparing group D and E(5 and 10 units oxytocin bolus) group-D showed most optimal uterine contraction 61.3% cases in comparison to commonly used 10 units bolus dose (group-E) 48.4% cases, with minimal side effects like, less tachycardia(12.9% versus 72.9%) and hypotension (12.9% versus 32.3%), while no top-up bolus doses were needed in 54.8% cases(group-D) and 48.8%(group-E) cases and no complain of epigastric discomfort observed in group-D, whereas in group-E epigastric discomfort was noted in 3.2% of cases respectively. The systolic and diastolic blood pressure in relation to oxytocin bolus dose mean (Std. deviation), heart rate from 1-10 minutes of syntocinon bolus, is shown in table-1 and 2 respectively. The heart rate variability in reference to baseline on administering bolus oxytocin dose is graphically shown for the initial two minutes in graph-1. In detail study parameters noted in different groups are depicted in table-3. In this study no top-up was needed in the ongoing oxytocin infusion in all cases.

DISCUSSION:

Oxytocin has been widely used since decades in caesarean sections for promoting uterine contraction and to prevent post-partum hemorrhage. Oxytocin is a naturally occurring peptide hormone that is synthesized in the para ventricular nuclei of the hypothalamus and from here it is transported in secretory granules to the posterior pituitary and then it is released as per requirement of body. It has two main effects: uterine contraction and milk ejection from the lactating mammary gland. [25]Review of literature show numerous doses finding studies regarding use of oxytocin in caesarean section. Butwick AJ and colleagues compared oxytocin in

Table-1: Hemodynamic variables after oxytocin bolus. (n=155)

Systolic / diastolic blood pressure (mmHg) Related to oxytocin intra-venous bolus						
Time interval	Baseline	1 minute	2 minutes	3 minutes	6 minutes	10 minutes
Mean	113.52 / 64.83	107.00 / 58.96	109.99 / 60.53	110.36 / 60.74	110.08 / 59.63	110.28 / 60.35
Std. deviation	16.708 / 14.519	17.81 / 15.91	16.58 / 12.83	14.22 / 13.40	14.44 / 13.26	13.54 / 12.91

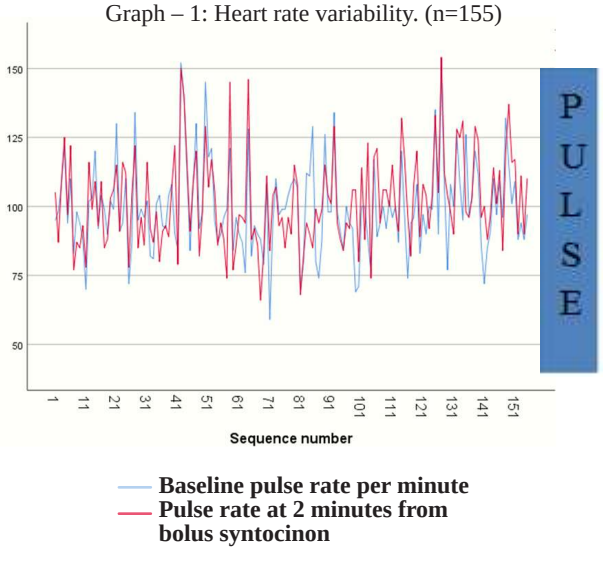
Table-2: Heart rate parameters after oxytocin bolus. (n=155)

Heart rate (per minute); related to oxytocin intra-venous bolus					
Time interval	Baseline	1 minute	3 minutes	6 minutes	10 minutes
Mean	99.48	105.74	99.24	98.72	98.66
Std. deviation	16.51	17.03	16.43	16.18	15.97

Table-3: Parameters noted in different groups. (n=155)

Bolus of oxytocin	Group-A (0.5 IU)	Group-B (1 IU)	Group-C (3 IU)	Group-D (5 IU)	Group-E (10 IU)	P-value
Mean age(years)	28.4	29.6	28.7	27.4	28.6	
Adequate uterine contraction	54.8%	35.5%	54.8%	61.3%	48.4%	0.314
Tachycardia after bolus	3.2%	6.5%	3.2%	12.9%	72.9%	0.38
Hypotension after bolus	9.7%	12.9%	19.4%	12.9%	32.3%	0.136
Epigastric discomfort after oxytocin bolus	0%	0%	6.5%	0%	3.2%	0.245
Top ups of oxytocin (once only)	51.6%	35.5%	29%	22.6%	35.5%	0.687
Top ups of oxytocin (more than once)	6.4%	22.6%	16.1%	10%	16.1%	
No top-up required	42%	41.9%	54.8%	54.8%	48.4%	

Graph – 1: Heart rate variability. (n=155)



boluses of zero(placebo group),1 ,3 ,5 IU soon after delivery of baby followed by infusion of 5 IU /hour and at two minutes uterine tone was assessed that was same in all groups and 66 % in placebo group, however half of the patients in placebo group needed rescue oxytocin. None of the patients in 3 and 5 IU group required rescue oxytocin probably because uterine massage was also done in this study. The estimated blood loss was similar in all groups of this study which depicted that adequate uterine tone can be achieved with low doses of oxytocin.[26]

Qian XW, et al. did a dose (ED 95) finding study of oxytocin infusion in 150 patients. All patients received oxytocin bolus of 1 unit soon after delivery of baby followed by infusion of 0,1,2,3,5, or 8 IU /hour as per category of patient. Uterine tone was assessed by gynecologist as adequate or inadequate requiring top up bolus of oxytocin. In this study ED 95 was estimate to be 7.72 IU. No difference was noted regarding oxytocin dose related side effects. This study suggested that dose of oxytocin required in post-partum period can be reduced if given as an infusion followed after bolus.[27] This regimen was adopted in our study.

Beiranvand S and colleagues in study stated that minimum effective dose of oxytocin in non-laboring patients was 1 unit and in laboring patients it was 1.5 unit.[28] A study by Shashikiran and colleagues to determine minimum effective dose of oxytocin during cesarean delivery in high risk cases of uterine atony concluded that 0.405IU / min infusion of oxytocin was adequate and higher doses did not result in further improvement of uterine tone.[29] In study by Keikhaie KR and colleagues[30] stated in their study that high dose oxytocin infusion is needed to prevent atony and post-cesarean bleeding with no major side-effects.

Few limitations in our study were that variations in response to oxytocin that might be present with respect to history of previous caesarean sections and multi gravidity. The rescue bolus doses of oxytocin were incorporated in our study design to reduce the risk of uterine atony or bleeding for patients with in-adequate uterine tone as intra-venous bolus oxytocin has a short half-life of 4-10 minutes. We recognize that uterine tone assessment in our study was affected by use of rescue bolus doses. The subjective nature of uterine tone assessment by obstetrician in our study though a limitation but this assessment is in line with current obstetric practice until a more accurate tool is available for assessing uterine tone.

CONCLUSION:

It was concluded that low doses of oxytocin are as effective as high doses in terms of uterine contraction with minimal side effects

Author Contribution:
Muhammad Salman Maqbool: Concept, Study Design, Planning, Experimentation, Study conduction, Drafting, Manuscript Writing, Data Analysis, Interpretation, Discussion, Critical Review, Final Approval of version
Ayesha: Concept, Study Design, Planning, Experimentation, Study conduction, Drafting, Manuscript Writing, Data Analysis, Interpretation, Discussion, Critical Review
Huda Shafqat: Concept, Study Design, Planning, Experimentation, Study conduction, Drafting, Manuscript Writing.

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Original Article

Evaluation of Candidal Carriage Among Smokers and Non-Smokers

Umar Irfan, Salik Rasool, Perveen Memon, Shazia Irum, Bushra Jabeen, Faraz Khan

ABSTRACT

Objectives: To determine the *Candidal* carriage among smokers and non-smokers and with different intra-oral sites including examination of various biotypes of *Candida*.

Study design and setting: Cross-sectional based study conducted at Dr. Ishrat ul Ebad Khan Institute of Oral Health Sciences and Dow International Dental College, Karachi, from May 2017 till April 2018.

Methodology: Comprised 100 patients (50 smokers and 50 nonsmokers) between 20 and 60 years of age. The collection was performed through sterile cotton swab to evaluate oral *Candidal* carriage and the colonizing *Candida* species using Sabouraud Dextrose Agar (SDA) and API20C AUX (BIOMERIEUX). Data was analyzed Spss version 20.

Results: A total of 100 participants (50 smokers and 50 non-smokers) were evaluated for *candidal* carriage. The common age group was 20-30 years in both the groups, without significant difference (p-value 0.79). Frequency of *candidal* carriage was comparable among smokers 14 (28.0%) to non-smokers 10 (20.0%), with a statistically insignificant p-value 0.35. Based on various biotypes among smokers and non-smokers, *Candida albicans* was 9(18%) and 7(14%), *Candida glabrata* was 4(8%) and 2(4%); and *Candida tropicallis* was 1(2%) each for both smokers and non smokers. Dorsum of tongue harbored all prevalent biotypes i.e. *Candida albicans*, *Candida glabrata and Candida tropicalis* as statistically significant among smokers (p-value 0.04).

Conclusion: Candidal carriage was comparable among smokers and non-smokers. *Candida albicans* and *Candida glabrata* were the common biotypes predominantly among smokers.

Key Words: *Candida albicans*, Oral cavity, Tobacco smoking.

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INTRODUCTION:

Fungi are aerobic micro-organisms.[1]The major human fungal pathogens belong to genus *Candida*, mainly *Candida albicans*, which causes different types of infections in humans. Infections caused by *Candida albicans* frequently affect the immunocompromised patients.[1]

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Oral *Candida* species, mainly *Candida albicans* are frequently isolated from the oral mucosa of humans, with oral carriage prevalence varying between 17-75% in all healthy individuals[2], mainly the children and younger adults[3]. The increased risk factors for oral candidal carriage in humans documents age, female gender, pregnancy, wearing of dentures, immune suppression, hypo-vitaminosis, iron deficiency, steroid treatment, poor oral hygiene[2-4], xerostomia, salivary pH[5] and systemic diseases, such as chronic hyperglycemia.[2-4]

During the recent years, there has been a dramatic increase in fungal infections, mainly due to increase in number of immunocompromised patients, such as patients infected with HIV and patients undergoing chemotherapy due to cancer[3]. It has been noted that bio-films associated with denture stomatitis is not only caused by *Candida Albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, *Candida parapsilosis* and *Candida dubliniensis* are the additional risk factors for the disease.[3] The use of tobacco has been considered as the most common risk factor for development of oral candidal infections.[2-3] According to World Health Organization (W.H.O), it is estimated that the use of tobacco will turn out to be single most common health leading problem by the year 2020.[6-7] It accounts for six million deaths yearly[8], which is expected to cause more than 8 million deaths annually by the year 2030.[8-9]

The effects of cigarette smoke on the oral mucosa are both chemical and thermal. Use of tobacco is a primary cause of many oral diseases and adverse oral health conditions. Studies conducted in some industrialized countries have shown that smoking alone is responsible for more than half of the periodontitis cases in adults.[5,6,8,9,10]

Some studies showed that cigarette smoke cause increased *Candida albicans* adhesion and growth as well as biofilm formation in association with increased secretion of proteolytic enzymes, particularly aspartyl proteinases[2,4,10]. Additionally, other studies have reported that *Candida* increases epithelial atypia and leads to epithelial hyperplasia and malignant conditions.[2]The significance of identifying *Candida* species is important for understanding the epidemiology, pathogenicity as well as treatment of oral *Candidiasis.*

To date, there is insufficient data regarding the candidal carriage in local population among the smokers and non-smokers.

The objectives of this study was to determine the *Candidal* carriage among smokers and non-smokers and with different intra-oral sites including examination of various biotypes of *Candida.*

METHODOLOGY:

This cross sectional study was conducted at the department of Oral diagnosis outpatient department at Dr. Ishrat Ul Ebad Khan Institute of Oral Health Sciences, and Dow International Dental College, DUHS Karachi. The study duration was from May 2017 to April 2018. This research was conducted under ethical consideration. The internal board review of D.U.H.S approved the consent form and research protocol. The participation was voluntary and informed consent was obtained before being included in the study. Using PAS v11, two groups with a sample of 50 each with 95% power to identify the difference between the group proportions. Under the null hypothesis and alternate hypothesis the proportions in the groups are 0.325 and 0.675 respectively at the level of significance 0.05.[5]

The participants between the age of 20-60 years were included comprising of 50 smokers and 50 non-smokers in each group. Samples of participants were taken using the criteria of Canadian Tobacco Use Monitoring Survey-2015 (CTUMS). Convenient sample technique was used. The participants who were smokers were inducted in the study group and every non-smoker was inducted in control group. Exclusion criteria were immunocompromised patients, patients on antibiotics corticosteroids, antiglycemic agents, blood pressure medicines (known to alter candida microbiota), xerostomia any other white lesion other than candidiasis, denture wearers and orthodontic treatment cases.

The study parameters were based on the following factors; age, gender, smoking, candidal carriage, oral site and biotypes.

The participants were advised not to eat or drink for at least 2 hours. A sterile cotton-tipped swab was used. The samples were then collected from dorsal surface of tongue, commissural and buccal mucosae. (The reason for collecting the sample from these sites is due to the fact that the anatomy of the tongue favors the accumulation of carbohydrates which allows a favorable environment for candida growth as compared to the other intra-oral sites, e.g., buccal mucosae and commissural mucosae.) The swab samples were then placed in a glass tube, transported to the Department of Pathology, Dow Diagnostic Reference and Research Laboratory, Ojha Campus, Dow University of Health Sciences, Karachi and inoculated directly onto Sabouraud Dextrose Agar plates (SDA).The samples were then incubated for 24-48 hours at 37°C. The cultured plates were then visually examined for detection of whitish creamy growth of yeast like colonies of *Candidal* biotypes. Gram staining of colonies was done with gram-positive and gram- negative controls. The identification of gram-positive yeast like colonies was further processed for species level identification by inoculation on API 20C AUX (BIOMERIEUX) with standard McFarland. Sabouraud dextrose agar plates (SDA) and I20C AUX (BIOMERIEUX) kits for the evaluation of Candidal carriage were used as this is most the relevant technique and widely accepted.

Sabouraud Dextrose Agar (SDA) was prepared by the following method:

- Suspend 65g of Sabouraud in 1L of distilled water, add polysorbate (tween-80), and boil to dissolve completely.
- Sterilize by autoclaving at 121^0C (15lb pressure) for 15mins.
- Dispense 15ml amount in Petri dish.
- Allow it to solidify at room temperature. Final pH should be between 5.6-6.2 at 25^0C (room temperature).

Strip preparation:

- To obtain a humid atmosphere, an incubation box was prepared with lid and tray. It was filled with approximately 5ml of distilled water into the honeycombed wells of the tray.
- On the elongated flap of the tray, recording of the strain reference was performed.
- The strip was placed in the incubation tray after its removal from individual packing.

Preparation of inoculum:

- An ampule of NaCl 0.85% was used.
- A portion of yeast colony was obtained using a pipette by suction and a turbidity equal to 2 McFarland of a suspension was achieved.
- Finally, 2-4 drops of previous suspension was added into a newly opened ampule of C. medium.

Strip inoculation:

- The cupules are then filled with the obtained suspension in the ampule of C. medium.
- The lid is incubated at 30^0C for 48-72 hours after placing it on the tray.

Strip recoding:

- Compared the growth in each capules after the incubation period of 48 hours. It is a negative control. When control is less turbid than the cupules it indicates a positive reaction.

Identification:

- On the result sheet, using the profile index the reaction pattern was coded into a numerical profile. 3 groups were made to separate the tests and a number 1, 2 or 4 was marked for each group. A 7-digit number was obtained by adding numbers corresponding to positive reactions within each group. A 7-digit number created a numeric profile.

When a positive result with a value of 4 was obtained, the 21st test was done by the presence of hyphae (mycelium) or pseudohyphae (pseudo mycelium).

The data was analyzed on SPSS version 20. Frequency, Mean and Standard deviation were used as descriptive statistics. Chi-square test was implied for assessing the association of *Candidal* carriage and comparing the amount of *Candidal* carriage between smokers and non-smokers.

RESULTS:

A total of 100 participants that included 50 smokers and 50 non-smokers were investigated for possible Candidal carriage. Mean age of smokers was 30.10+10.20 years and non-smokers were 32.82+10.26 years. The most common age group was 20-30 years among both groups. Table 1. Regarding Candidal carriage distribution in terms of different intra-oral site, dorsal commissural buccal was the most common 6(12.0%) among smokers and 5(10.0%) among non-smokers, followed by dorsal commissural, buccal commissural, buccal dorsal and dorsal with percentage of 4.0%, 2.0%, 8.0% and 2.0% respectively among smokers and dorsal commissural, buccal commissural, commissural and buccal with percentage of 4.0%, 2.0%, 2.0% and 2.0% respectively among non- smokers.

According to the various biotypes among smokers and non-smokers, *Candida albicans* had a comparatively higher prevalence in smokers than non-smokers. Further details are given in Table 2. Regarding distribution of various biotypes according to buccal mucosa, *Candida albicans* was found among 6(12.0%) smokers and 5(10.0%) of non-smokers. *Candida glabrata* found among 3(06.0%) smokers and 2(04.0%) non-smokers. *Candida tropicalis* was only in 1(02.0%) smokers and 1(02.0%) non-smokers respectively, while there was no growth on buccal mucosa among 40(80.0%) smokers and 42(84.0%) non-smokers.

In terms of distribution of various biotypes according to commissural mucosa, *Candida albicans* was found among 5(10.0%) smokers and 6(12.0%) of non-smokers. *Candida glabrata* found among 3(06.0%) smokers and 1(02.0%) non-smokers. *Candida Tropicalis* was only in 1(02.0%) smokers and 1(02.0%) non-smokers respectively, while there was no growth on commissure mucosa among 41(82.0%) smokers and 42(84.0%) non-smokers.

Considering the distribution of various biotypes according to dorsum of tongue, *Candida Albicans* was higher in smokers than non-smokers. Further details are given in **Table 3**.

DISCUSSION:

Oral *Candida albicans*, is the most frequently isolated biotype from the oral cavities. W.H.O estimates that around 22% of the people over 15 years age worldwide consume smokeless tobacco which is a public health concern[21]. Our study results showed that frequency of *Candidal* carriage was high among smokers 14(28%), in contrast to non-smokers 10(20%), with a statistically insignificant p-value of 0.349. Similarly, in a study conducted by Darwazeh et al.[5,12,15] showed that the rate of *Candida* carriage was 84% in smokers and 74% in the non-smokers. In another study conducted by Keten et al, stated that *Candidal* infection was present in 58.3% of smokers (P = 0.018)[22]. Some studies have revealed a signi?cantly higher rate of *Candidal* carriage in the smokers compared with non- smokers[15]. The significance of identifying *Candida* species is important for understanding the epidemiology, pathogenicity and treatment of oral *Candidiasis*[16]. Several studies have, on the other hand reported that tobacco smoking either alone or in combination with other factors, is associated with increased

Table 1: Demographic characteristics of smokers and non-smokers n=100

Variables	Groups		P-value*
	Smokers	Non–smokers	
Age groups			0.786
20-30 years	22(44.0%)	25(50.0%)	
31-40 years	17(34.0%)	14(28.0%)	
40-60 years	11(22.0%)	11(22.0%)	
Total	50(100.0%)	50(100.0%)	
Intra-oral sites			0.398
DCB	6(12.0%)	5(10.0%)	
DC	2(4.0%)	2(4.0%)	
CB	1(2.0%)	1(2.0%)	
BD	4(8.0%)	00	
D	1(2.0%)	00	
C	00	1(2.0%)	
B	00	1(2.0%)	
Not found	36(72.0%)	40(80.0%)	
Total	50(100.0%)	50(100.0%)	
Candidal carriage			0.349
Yes	14(28.0%)	10(20.0%)	
No	36(72.0%)	40(80.0%)	
Total	50(100.0%)	50(100.0%)	

Mean age = 30.10+10.20 years of smokers and 32.82+10.26 years of non-smokers *chi-square

Table 2: Various biotypes among smokers and non-smokers n=100

Various biotypes	Groups		P-value*
	Smokers	Non–smokers	
No growth	36(72%)	40(80%)	0.711
Albicans	9(18%)	7(14%)	
Glabrata	4(8%)	2(4%)	
Tropicalis	1(2%)	1(2%)	
Total	50(100%)	50(100%)	

*chi-square

Table 3: Various biotypes in dorsum of tongue in smokers and non-smokers n=100

Biotypes of Candida	Dorsum of tongue		*P*-value*
	Smokers	Non–smokers	
No growth	37 (74%)	47 (94%)	0.044
Albicans	09 (18%)	01 (2%)	
Glabrata	03 (6%)	01 (2%)	
Tropicalis	01 (2%)	01 (2%)	
Total	50 (100%)	50 (100%)	
Biotypes of Candida	**Commissural mucosa**		***p*-value**
	Smokers	**Non–smokers**	
No growth	41 (82%)	42 (84%)	0.776
Albicans	5(10%)	6 (12%)	
Glabrata	3 (6%)	01 (2%)	
Tropicalis	01 (2%)	01 (2%)	
Total	50 (100%)	50 (100%)	
Biotypes of Candida	**Buccal Mucosa**		***p*-value**
	Smokers	**Non–smokers**	
No growth	40 (80%)	42 (84%)	0.952
Albicans	6(12%)	5 (10%)	
Glabrata	3 (6%)	2 (4%)	
Tropicalis	1 (2%)	1 (2%)	
Total	50 (100%)	50 (100%)	

*chi-square

Figure 1: **(a)** *Candida albicans* on dorsal surface, B= *Candida albicans* on buccal surface, C= No growth on commissural surface **(b)** *Candida tropicalis* on dorsal surface, B= *C. tropicalis* on buccal surface, C= *Candida tropicalis* on commissural surface **(c)** C. *albicans* on buccal surface, B= no growth on buccal surface, C= *C. glabrata* on commissural surface

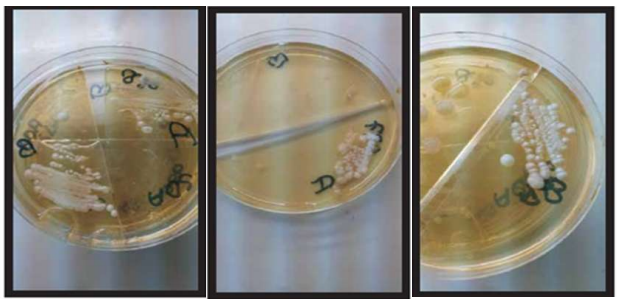
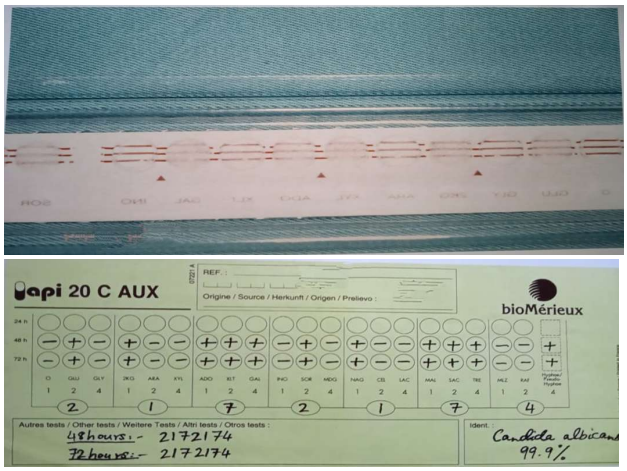


Figure 2**: (a)** Turbid and non turbid honey comb wells give a 7digit value. (**b)** 7 digit API Aux coding sheet positive for *candida albicans*



incidence of oral *Candida* colonization[14,17,19] and the relationship between frequency of smoking and the *Candidal* carriage is proportional[18,21,23]. In our study, a total 100 participants 50 smokers and 50 non-smokers were investigated according to *Candidal* carriage. Mean age of smokers was 30.10+10.20 years and non-smokers were 32.82+10.26 years, showed no significance (p-0.786). On other hand Keten et al, also reported that the mean age of the participants was 40.49 ± 12.89 years[21].

Regarding our study on distribution of various biotypes according to buccal mucosa, *Candida albicans* was found among 6(12%) smokers and 5(10%) of non-smokers. *Candida glabrata* found among 3(6%) smokers and 2(4%) non-smokers. *Candida tropicalis* was only in 1(2%) smokers and 1(2%) non-smokers respectively, while there was no growth on buccal mucosa among 40(80%) smokers and 42(84%) non-smokers, p-value 0.952. Keten et al12,16,19, reported that the most frequently isolatedÊ*Candida*Êspecies in all groups wereÊ*C. albicans*, followed byÊ*C. tropicalis*, in the present study. Consistently, it has been reported in the literature that the most frequently isolated oralÊ*Candida*Êspecies wasÊ*C. albicans*Êfollowed byÊ*C. tropicalis*Êboth in smokers and the normal population[5-10]. Frequency among commissural mucosa, *Candida albicans* was found among 5(10%) smokers and 6(12%) of non-smokers. *Candida glabrata* found among 3(6%) smokers and 1(2%) non-smokers. *Candida tropicalis* was only in 1(2%) smokers and 1(2%) non-smokers respectively, while there was no growth on commissure mucosa among 41(82%) smokers and 42(84%) non-smokers. Rodrigues et al, reported *Candida albicans* was the most common species (80.9%) frequently isolated from the tongue and buccal surface, followed by *C. tropicalis* (7.2%) frequently isolated from the tongue and palate[12,16,19]. Darwazeh et al, reported *Candida albicans* as (65%) frequently isolated from the tongue and commisure, followed by *C. tropicalis* (11%) frequently

isolated from the tongue[17,19,23,24].

Considering the distribution of various biotypes according to dorsum of tongue, *Candida albicans* was higher in smokers than non-smokers[14,20,25].

The research project had some limitations that have been addressed. Firstly, the participants in the study were only males, females were not included in the study. Secondly, quantification of oral candidal species was not done. Thirdly, the study was conducted on a limited population of Karachi and only two public sector hospitals were selected due to limitation of resources and budget. Fourthly, no ethnicity was taken into account, as candidal carriage may vary between various ethnic groups.

CONCLUSION:

It was evident that the candidal carriage was significantly high among smokers, compared to non-smokers. *Candida albicans* and *Candida glabrata* were the most common biotypes and found mainly among the smokers. Commissural mucosa and buccal mucosa were the most commont intraoral sites.

Author Contribution:
Umar Irfan: Introduction and Methodology
Salik Rasool: Discussion
Perveen Memon: Lab work
Shazia Irum: Lab work
Bushra Jabeen: Statistics
Faraz Khan: Results

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Original Article

Expression of BRAF V600E in Tissue Samples of Colorectal Carcinoma and Its Correlation with Various Clinico-Pathological Parameters

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ABSTRACT

Objective: To determine the expression of BRAF V600E in tissue samples of colorectal carcinoma and to correlate it with various clinico-pathological parameters.

Study design and setting: Cross-sectional study was conducted at department of Pathology, Pakistan Navy Station Shifa hospital Karachi from 1st March 2016 to 28th February 2019

Methodology: Total of 51 cases of colorectal cancer were analyzed for immunohistochemical staining using BRAF antibodies on representative tissue blocks. Clinical and pathological records were retrieved for data collection. The results of immunohistochemical analysis were correlated with the recorded clinico-pathological parameters.

Results: In this study 51 cases of colorectal cancer were analyzed for immune expression of BRAF V600E. The age of the patients ranged from 14 to 85 years with the mean age of 60.96 years. Among the 51 cases, 37(72.5%) cases were males and 14(27.4%) were females. 37(72.5%) were localized to left side colon and 14(27.4%) were found in the right colon. For BRAF V600E, positive expression was seen in 20(39.2%) cases, whereas 31(60.7%) cases showed negative expression of BRAFV600E. No significant association was seen between BRAF V600E expression and histological variants like age, gender, tumor location and glandular carcinomas.

Conclusion: BRAF V600E immunosuppression was seen in 39.2% of colorectal carcinoma in this study. No significant association was seen in BRAF V600E expression and histological variants.

Key Words: BRAF V600E Immunohistochemistry, Colorectal cancer, Clinicopathological parameters.

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INTRODUCTION:

Colorectal cancer (CRC) has been identified as the most common cancer of the digestive tract. Being the third most prevalent cancer in both genders. It represents almost 10% of all registered malignant diseases.[1,2] Estimated incidence levels in males for colorectal cancer is significantly greater than in females in major areas of the globe. Recently, a large number of developing countries have shown an acute increase in the incidence of colorectal cancer.[3] In Pakistan CRC accounts for 52% of all gastrointestinal tumors in comparison to other countries.[4]

Colorectal cancer (CRC) is a heterogeneous disease which emerges through several important pathways. Both environmental and genetic factors are responsible for the development of the pathogenesis.[5] However there is a continuous rise of colorectal carcinoma in those under the age of 50.[6] Several genetic and epigenetic mutations have been identified in various proto oncogenes and tumor suppressor genes which involve distinct pathways like, chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylation phenotype (CIMP).[7, 8]

The most commonly occurring mutation in colorectal carcinoma is gain in the function of BRAF proto-oncogene, which act as potent carcinogens in initiation and progression of colorectal carcinoma and plays a significant role in its pathogenesis. BRAF belongs to RAF family of protein and its gene is located on chromosome 7, encoding a 766-amino acid serine/threonine kinase.[9] The vast majority of mutated BRAF is V600E resulting from a point mutation having 80% cancerous potential. This results in constitutive activation

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of RAS-RAF-MAPK pathway. BRAFV600E significantly increases the DNA methylation of CIMP-associated markers in primary colorectal tumors. BRAF V600E mutations are assumed an early event in serrated pathway of tumourigenesis. 60% of BRAF mutated tumors have association with MSI CRC. BRAF V600E mutations in colorectal carcinoma are connected with older age group, mainly occurs in female gender.[10] It has been revealed that mutation of BRAF such as V600E is closely linked with tumors of proximal colon, mucinous histology and poor differentiation. BRAF mutated tumors are often right sided in contrast to the KRAS mutations which are largely associated with left sided CRC.[11,12] The expression of V600E mutated BRAF can be explored by immunohistochemistry using VE1 i.e. BRAF V600E mutation-specific antibody. Also early screening of BRAF V600E might improve the evaluation of the risks for colorectal cancer and may help in effective management of the patients. IHC additionally offers the benefit of a quicker, faster and easy to perform assay in comparison to molecular testing and it can be successfully and productively used in the diagnostic setting.[13] It has been suggested that immunohistochemical detection of BRAF V600E in routine clinical laboratories can be used as an alternate method to molecular testing and can be recommended as an accurate, easily interpreted and less time consuming technique.

Therefore VE1 immunohistochemistry may act as a helpful tool in the screening for colon carcinomas associated with BRAF mutation but the status of mutation of BRAF should always be validated by molecular genetic studies.[14] Moreover the BRAF V600E mutation has been appraised as an early event in colorectal cancer with multifaceted roles for progression, diagnosis and the prognosis of colorectal cancer.[15]

Limited data is available with regards to the expression of BRAF V600E in colorectal carcinoma in Pakistani population. Hence, this study aimed at evaluating expression of this marker in our population and to correlate it with various clinicopathological features in order to aid selection of effective treatment options.

METHODOLOGY:

This Cross sectional observational study was based on the analysis of colonic biopsies received in the Department of Pathology, PNS Shifa hospital Karachi from March 2016 to March 2019. Ethical approval letter with reference No : ERC 42/2018 was issued by the Ethical Review Committee of Bahria University Medical and Dental College. Informed consent was signed by every patient before enrollment in the study.

The samples were collected including both biopsies and colectomy specimens. Sample size was calculated using software G-POWER (version 3.1.9.2) by taking 95% confidence interval, 5% margin of error. The required sample size was found to be 51. All colonic surgical specimens diagnosed as primary colorectal carcinoma obtained prior to therapy and patients who were willing to participate in the study were included, whereas poorly fixed tissue, inadequate material, metastatic tumors, post radiotherapy specimens as well as patients who refused to participate in the study were excluded from this research.

During the study period, from March 2016 to March 2019, 291 colorectal samples were received at our setup. Both biopsies (n=29) and colectomy specimens (n=22) were analyzed for histopathological diagnosis. Among them 240 cases were reported as benign lesions while 51 cases were diagnosed as colorectal cancer. Hematoxylin and eosin as well as anti-BRAF V600E immunohistochemical staining was performed on the formalin-fixed paraffin-embedded (FFPE) tissues. The clinicopathological data including age, sex, location, microscopic types, and histological grade were collected for statistical analysis. For immunohistochemistry sections of 3 to 5µm thickness were taken from FFPE tumor blocks picked on poly-L-lysine coated slides. was done using retrieval solution (pH 6.0 citrate buffer 10 x) in water bath at 98-99 º C for 40 minutes. Container was removed from water bath and then cooled at room temperature (15 to 20 minutes). Retrieval solution was discarded and section was rinsed two to three times. Endogenous peroxidase was blocked using hydrogen peroxide blocking solution Primary antibody was applied to cover the section. BRAF V600E dilution was done in the ratio of 1:20 as per company provided protocol. After several washing steps in PBS, sections were incubated for 30 min with labeled second antibody. DAB substrate chromogen solution (1 ml substrate buffer + 1 drop DAB chromogen) was applied to cover section, incubated for 2 minutes, washed and counterstained with hematoxylin, dehydrated with ethanol, cleared in xylene and mounted. The slides were then visualized under a light microscope. Tissue samples to which no primary antibody had been added were used as negative controls.

Immunoreactivity was scored by taking into account the percentage of stained tumor cells (Yellow brown color) and intensity of staining. For BRAF V600E, the intensity of cytoplasmic tumor cell staining was scored as weak (1), moderate (2) and strong (3). The cytoplasmic staining of BRAF V600E of at least medium intensity in more than 10% of tumor cells was considered as positive, while the tumors were considered immune negative when there was weak staining or there were less than 10% of stained tumor cells. Papillary thyroid carcinoma with a documented BRAF V600E mutation was used as a positive control. Statistical analysis was done using SPSS version 23.0 Continuous variables were presented as mean and standard deviation. Categorical variables were presented as frequency and percentage. Chi-square and Fisher exact test were used to assess the association of BRAF expression with different clinicopathological parameters. P=0.05 was considered statistically significant.

RESULTS:

In this study 51 cases of colorectal carcinomas were included, among them 16 showed mucinous histology with signet ring cells, 1 showed cribriform pattern, 2 were poorly cohesive tumors, while the rest 32 were adenocarcinomas.

Table-1 showed the immune expression of BRAF V600E protein in cases of colorectal carcinoma. Among the 51 cases subjected to BRAF V600E immunostaining, a total of 20 cases showed positive immune expression for mutated BRAF protein, while remaining 31 cases were negative for BRAF V600E.

Intensity and extent of immune expression of BRAF V600E protein in diagnosed malignant cases of colorectal samples. The positivity was strong (3+) in 7 cases, moderate (2+) in 13 cases-Table-2. The remaining 6 cases showed weak staining intensity with BRAF V600E protein on immunohistochemistry. Total 7 cases revealed strong staining for BRAF V600E protein, 6 cases showing strong reactivity in ?75% of tumor cells and only 1 case showed strong reactivity in almost 50% of tumor cells.

Table-3 correlates the expression of BRAF V600E with different clinicopathological parameters. Out of 37 male patients, 13 cases showed positive expression, while remaining 24 cases showed no expression of BRAF V600E. In female gender 7 out of 14 cases showed no expression of this protein while remaining 7 cases showed positive expression for BRAF V6000. 14 out of 37 left sided lesions showed positive expression of BRAF V600E, while 23 cases were negative for BRAF V600E expression. Among 14 malignant cases from the right colon, 8 cases had no protein expression while remaining 6 cases revealed expression of mutated BRAF protein. 14 out of 32 cases of glandular adenocarcinoma, showed moderate to strong BRAF V600E expression, whereas remaining 18 cases showed no expression.

In this study 16 cases of colorectal carcinoma had mucinous histology with signet ring type cells. Among them 5 cases revealed no protein expression whereas remaining 11 cases showed positive BRAF V600E expression. 2 cases were diagnosed as poorly cohesive and one as having cribriform pattern. Among these only one case of poorly cohesive carcinoma revealed positive BRAF V600E expression on immunohistochemistry.

Table 1: Expression of BRAF-V600E in colorectal carcinoma (n=51)

BRAF-V600E Expression	No of cases of colorectal carcinoma (%)
Positive expression	20 (39.2 %)
Negative expression	31 (60.8%)

Positive expression: cytoplasmic staining of at least medium intensity in more than 10% of tumor cells
Negative expression: tumors were considered immune negative when there was ?10% of stained tumor cells.

DISCUSSION:

This study was aimed to determine the frequency of colorectal cancers received at our setup and to study the expression of BRAF V600E in these cases and to evaluate its effects on colorectal carcinogenesis to select effective treatment options.

In the present study the mean age for colorectal carcinoma was found to be 60.96 years. These findings were in accordance with the figures documented in Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan.[16] According to which the estimated mean age for males and females were reported as 53 years and 50 years respectively.[16] A study conducted at Aga Khan University Hospital Karachi in 2014 which included 131 young patients, showed comparatively lower mean age which was documented as 33.3years. This distinction may be attributed to the sample size variation.[17] Similar results were reported in a study showing that colorectal cancer was diagnosed in 65.8% male and 34.2% of female patients.[18]

In the present study most commonly observed grade was well differentiated adenocarcinoma, whereas the common

Table 2: Intensity and extent of BRAF-V600E in diagnosed cases of Colorectal Carcinoma (n= 26)

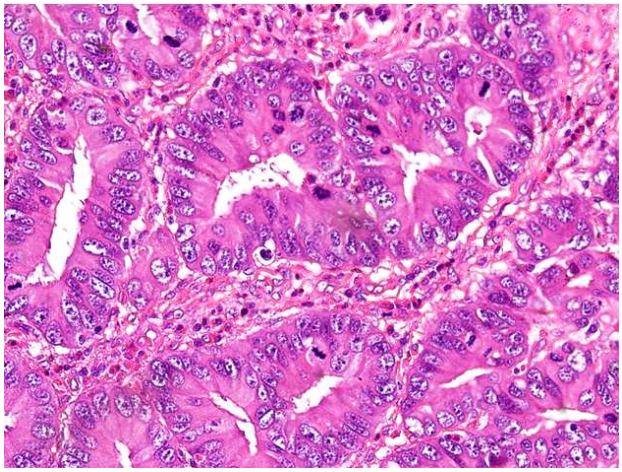
Immunostaining	Extent				Intensity			
	0	1	2	3	0	1	2	3
Weak	1 (16.6%)	2 (33.3%)	1 (16.6%)	2 (33.3%)	0 (0%)	6 (100%)	0 (0%)	0 (0%)
Moderate	0 (0%)	0 (0%)	4 (30.7%)	9 (69.2%)	0 (0%)	0 (0%)	13 (100%)	0 (0%)
Strong	0 (0%)	1 (%)	0 (0%)	6 (87.5%)	0 (0%)	0 (0%)	0 (0%)	7 (100%)

Extent of reactivity (% of immunoreactive nuclei) was as follows: 0, < 10%; 1+, 25-50%; 2+, 50-75%; 3+, >75%.
Intensity of reactivity was as follows: 0, no staining; 1+, weak staining; 2+, moderate staining; 3+, strong staining

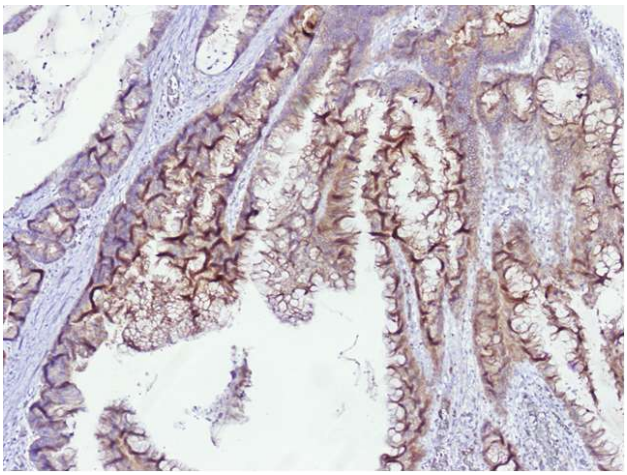
Table 3: Association of clinicopathological features with expression of BRAF-V600E expression (n=51)

Clinicopathogical Features	Total numbers	BRAF V600E		P-value
		Positive	Negative	
Gender	Male = 37	13	24	0.35
	Female = 14	7	7	
Tumor Location	Right-sided =14	6	8	0.758
	Left-sided = 37	14	23	
Glandular Adenocarcinoma	32 (62.7%)	14	18	0.862
Mucinous Carcinoma/Signet ring	16 (31.4%)	5	11	
Poorly cohesive	2 (3.9%)	1	1	
Ciribriform pattern	1 (2.0%)	0	1	

Photomicrograph 1: Colorectal adenocarcinoma H&E X 40



Photomicrograph 2: colorectal adenocarcinoma (same as in photomicrograph 1) showing moderate to strong expression of BRAF V600E in more than 90% of tumor cells. IHC X 20



microscopic variants were reported as adenocarcinoma, and mucinous-signet ring type carcinoma. Our findings corresponded to the figures documented in National Cancer Institute, Cairo University, Egypt (2013) which included 26 metastatic colorectal cancer cases in one study. In this study the histological variation were observed such as, adenocarcinoma, 22(84.6%) cases, mucinous carcinoma, 2(7.7%) cases and signet ring carcinomas, 2(7.7%) cases.[19]

In the present study out of 51 cases of colorectal carcinomas, 37 (72.5%) cases were present in males, while the remaining 14(27.4%) cases of colorectal cancer were seen in females.

With respect to BRAF V600E immune expression, out of 51cases, 20(39.2%) cases showed positive BRAF V600E expression, while remaining 31(60.8%) cases revealed no expression of BRAFV600E on IHC. These results are in agreement with other studies which concluded positive BRAF V600E expression on IHC, as well as on genetic analysis.[14, 20, 21, 22]

In this study we did not find significant correlation of positive expression of BRAF V600E with clinicopathological parameters like, age, gender, location, tumor grades and histological variants. These results are in accordance with a study which did not find any significant correlation between these parameters and BRAF V600E expression.[23, 24]

A study found that tumor stage is important for evaluating BRAF mutant tumors for treatment options. Early tumor stage may be prone to BRAF-specific inhibition alone, as tumor stage advances, various processes must be aimed owing to concentration of mutations. It has been suggested that RAF inhibitor combination strategies can suppress feedback reactivation of MAPK signaling pathway and improve efficacy in BRAF -mutant colorectal cancers.[25]

As the surrounding normal mucosa was also taken into consideration while assessing results of IHC, the study can give an idea regarding the expression of abnormal protein in early lesions also signifying BRAF mutation as a potential early change in tumorigenesis of these cancers.

Last but not the least the presence of BRAF V600E mutation in the current study stresses the need for using anti-BRAF V600E as a routine biomarker by IHC in colorectal carcinoma diagnosis and stresses the significance and importance of BRAF V600E inhibitors as a potential, alternate therapeutic tool in EGFR inhibitor and chemotherapy resistant tumors. The limitations of the study included data from single tertiary

care hospital and small sample size, therefore does not represent the general population. Further large scale multicentric studies will be required to assess the burden of mutations in our population. Additional, relevant clinical data could not be ascertained because of inaccessibility to the record files.ÊIt is strongly recommended that future preferably molecular studies should be conducted to evaluate BRAF V600E mutations as an early carcinogenic event in colorectal cancers. This study also provides a spring board for further studies as it may open venues for exploring new therapeutic options.

CONCLUSION:

BRAF V600E immunoexpression was observed 39. 2% of colorectal carcinoma cases. The expression of BRAF V600E in our population signifies the importance of introducing BRAF V600E as a valuable diagnostic biomarker for colorectal carcinoma. It further stresses the importance of BRAFV600E inhibitors as an alternate therapeutic option in EGFR inhibitor and chemotherapy resistant tumors. Furthermore, the positive BRAF V600E expression in normal mucosa adjacent to the tumor points toward BRAF V600E mutation as an early event in colorectal carcinogenesis.

Author Contribution:
Hina Wasti: Conceived idea, Study designed. Data collection, immunohistochemical analysis, Result interpretation, literature review, Manuscript writing.
Summayyah Shawana: Data analysis, Result interpretation, Proofreading, Manuscript writing & correction of entire Manuscript
Beenish Hussain Nomani: Data collection, immunohistochemical analysis & Proofreading of entire Manuscript
Santosh Kumar Sidhwani: Proofreading of Manuscript & helped to draft the manuscript
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Original Article

Self-Medication Among Undergraduate Students

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ABSTRACT:

Objective: To evaluate the frequency of self-medication among undergraduate students of medical sciences

Study design and setting: Cross-sectional Study was conducted at Al-Tibri Medical College Hospital, from October 2019 to February 2020.

Methodology: Data was collected after an ethical approval of concerned institute; total of 150 students included from the 1st, 3rd and final year of MBBS. Valid questionnaire was used to evaluate the response of the participants regarding self-medication. Verbal consent was taken from the students, and then they were asked to fill their responses. Data was evaluated in the form of frequency and percentages through SPSS version 21.0. Chi-square test was applied, and the level of significance was considered p=<0.05

Results: Out of total of 150 students, 58.7% were males and 41.3% females. In students of 1st, 3rd and 5th year the most common morbidity for seeking self-medication was headache, flu/cough, fever, and pain. The percentage of drug/ drug groups commonly used for self-medication included antipyretics being 36%, 54% and 64%, antibiotics were 50%, 86% and 90%, and analgesics was 42%, 62% and 64% in 1st, 3rd and 5th years respectively. Common reasons for pursuing self-medication were minor illnesses (50%, 81%, 94%), easy availability (52%, 82%, 92%) and quick-relief (50%, 58%, 100%) in 1st, 3rd and 5th year respectively.

Conclusion: In the present study, self-medication was observed in a large percentage of students. Thus, medical curricula need further consideration to promote awareness regarding the disadvantages of self-medication in undergraduates so we can curb this self-medication culture from our society.

Keywords: Drug, Medical sciences, Self-medication, undergraduate

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INTRODUCTION:

Medication is a term often practiced for medicines and pharmaceutical drugs intended for the treatment of several diseases. Unfortunately the trend of self-medication without prescription of physician has been widely under practice by people mostly to treat general health problems.[1] The practice of self-medication has been frequently noticed. The self-medicated drugs utilized regularly include analgesics, antipyretics, anti-emetics, and certain cough syrups.[2] Self-medication has been described by the WHO (World Health Organization) as humans being treated by selecting the medications by themselves in disguise for diagnosed diseases.[3] The practice of self-medication is increasing worldwide, especially reported in underdeveloped countries.[4] Many factors create a base in the progress of self-medication like drug availability, easy accessibility, and economic and cultural trends. In terms of psychological factors, the self-satisfaction level in people also contributes to self-medication worldwide. Rise in social, educational, economic status resulting from amended educational levels with vast approaches toward evidence and facts; and raising awareness of personal health is increasing their needs to take their resolution and decision for fitness.[5]

University students are more prone to the self-medication

practices discovered by several studies. [6] Due to the publicity of drugs by multiple pharmaceutical companies and diversities of advertisements increase their keenness to use the drugs. These students are utilizing the products without consulting any medical practitioner.[7] In addition to that, most university students use medicines with their previous experience which they might have used in the past for similar problems. Also by the opinion of some friends or colleagues have noticed some common problems noticed in students. Furthermore lacking time, unavailability of the transport system is also considered the issues which enhance the self-medication in the university students.[8] The practice of self-medication proportion rate under different areas, such as in Asia, becomes 4-7.5% that can be considered comparatively higher than that of Northern Europe, which is about 3%.[9]

Self-medication comprises of two divisions, distinctly divided from each other based on the practice of self-medication including responsible practice and the other being irresponsible one. When individuals are utilizing the medicines without any prescription, but under professional advice that could be readily available is called over-the-counter (OTC) drugs. According to the Saudi FDA, it is included in responsible self-medication practice. Another category that is very dangerous and creates problems worldwide is that the drugs are being used without medical practitioners' advice and not obtainable legally.[10]

The rationale was to educate the students and improve their curriculum based on the results. The study's primary purpose was to evaluate the frequency of self-medication among undergraduate students of MBBS. At first-year level, the knowledge of the students are not sufficient, however, moving to the higher levels, like in 3rd-year, pharmacology subject is part a curriculum so, the frequency of self-medication should be increase as compared to 1st year. For final years, they know the management and diagnosis, and the frequency of self-medication should be more than others.

METHODOLOGY:

A cross-sectional study was done at Al-Tibri Medical College and Hospital from October 2019 to February 2020. A total of 150 numbers of undergraduate students from MBBS, 1st, 3rd and 5th years were included after taking verbal consent. The data was collected by using a valid questionnaire[11]**;** was used for the evaluation of self-medication among the medical students of South India. The study was approved from ethical review committee numbered IERC/ATMC/19/46. The briefing of the questionnaire was given to the participants and both genders were included based on convenient sampling. Non-medical students and students from allied medical sciences were excluded from the study. Data were analyzed through SPSS version 21.0 and presented in the form of frequencies and percentages. The Chi-square test was applied, and $p<0.05$ was considered as statistically significant.

RESULTS:

In this study, 150 medical students of 1st, 3rd and final years were included in which male students were 88 (58.7%), and female students were 62 (41.3%). Table 1 shows frequency and percentage of indication for self-medication among undergraduates and level of significance. Figure 1 shows percentage of reasons for self-medication among undergraduate medical students. The results observed the significant differences among the different levels of students in all given reasons was <0.001. Figure 2 shows percentage of types of self-prescribed medicine among undergraduate medical students. The level of significance found in analgesics was 0.023, in antipyretic 0.016 as statistically significant. In prescribing antidiarrheals, antiemetics, antibiotics and sedatives the significant level observed with p-value was <0.001. While the self-prescribed antacids with p value of 0.05. Table 2 shows frequency and percentage of miscellaneous drugs that are commonly prescribed as self-medication. There was a significant difference in prescribing vitamin P= (<0.001), and insignificant difference was found in ophthalmic preparation with a p= 0.266 and p=0.066.

Data of the present study also assessed the precautions that should be taken during self-medication. Frequency and percentages of students idea about self-medication among the students of 1st year was 29(58%), 3rd year 41(82%) and 5th year about 46(92%) and there was a significant difference among the students p=<0.001. One of the main things is an idea about the complication of the self-prescribed drug which was in 1st-year students as 23(46%), 3rd years 29(58%) and final years 34(68%) respectively. There was no significant difference found among the students with a p value of 0.084, so there was uncertainty regarding the complication of prescribed drugs. Frequency and percentage of students that routinely check the insert of prescribed medicine was 32(64%) from 1st year, 44(88%) from 3rd year and 34(68%) from final year students with the significant difference among the students with a p value of 0.015. One of the important factors, checking of expiry date before use among first-year students was 36(72%), 44(88%) of 3rd year and 43(86%) from the final years. There was a significant difference found among the students with a p value of <0.001.

DISCUSSION:

Various studies have generally remarked on the pattern of self-medication. In this study, it was evaluated in undergraduate students of medical sciences from 1st, 3rd and 5th year students. It was estimated that the frequency of self-medication would be high in 3rd years and 5th-year students compared with 1st-year students as they know of medicines. These findings are equivalent to the study conducted in the medical college of West Bengal. [12] Another research on 2nd year and fourth-year students of Arabian Gulf University Bahrain also revealed the frequent use of self-medication among 4th-year students compared with 2nd years.[13]

Table 1: Indications for Self-Medication among undergraduate medical students

Symptoms	1st year		3rd year		5th year		P=value
Response	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	
Headache	30(60%)	20(40%)	45(90%)	5(10%)	45(90%)	5(10%)	**<0.001**
Cough/Flu	29(58%)	21(42%)	45(90%)	5(10%)	41(82%)	9(18%)	**<0.001**
Fever	29(58%)	21(42%)	38(76%)	12(24%)	41(82%)	9(18%)	**0.021**
Stomachache	13(26%)	37(74%)	31(62%)	19(38%)	36(72%)	14(28%)	**0.022**
Diarrhea	17(34%)	33(66%)	20(40%)	13(60%)	36(72%)	14(28%)	**<0.001**
Menstrual symptoms	2(4%)	48(96%)	23(46%)	27(54%)	16(32%)	34(68%)	**0.270**
Rash/Allergy	20(40%)	30(60%)	25(50%)	25(50%)	28(56%)	22(44%)	**0.014**
Anxiety	14(28%)	36(72%)	25(50%)	25(50%)	28(56%)	22(44%)	**0.012**
Ear problem	9(18%)	41(82%)	8(16%)	42(84%)	8(16%)	42(84%)	**0.953**
Vomiting	18(36%)	32(64%)	27(54%)	23(46%)	38(76%)	12(24%)	**<0.001**
Eye infection	6(12%)	44(88%)	18(36%)	32(64%)	16(32%)	34(68%)	**0.015**
Skin Problem	11(22%)	39(78%)	14(28%)	36(72%)	24(48%)	26(52%)	**0.013**
Toothache	8(16%)	42(84%)	17(34%)	33(66%)	34(68%)	16(32%)	**<0.001**
Insomnia	58(10%)	45(90%)	11(22%)	39(78%)	12(24%)	38(76%)	**0.151**
Pain	25(50%)	25(50%)	39(78%)	11(22%)	45(90%)	5(10%)	**<0.001**

Table 2: Miscellaneous Type of Self-Prescribed Medicine

Type of Drug	1st year		3rd year		5th year		P=value
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	
Vitamins	20(40%)	30(60%)	21(42%)	29(58%)	40(68%)	10(32%)	**<0.001**
Ophthalmic preparations	6(12%)	44(88%)	7(14%)	43(86%)	12(24%)	38(76%)	**0.226**
Cosmetic products	18(36%)	32(64%)	18(36%)	32(64%)	28(56%)	22(44%)	**0.066**

Figure 1: Reasons for Self-Medication among undergraduates

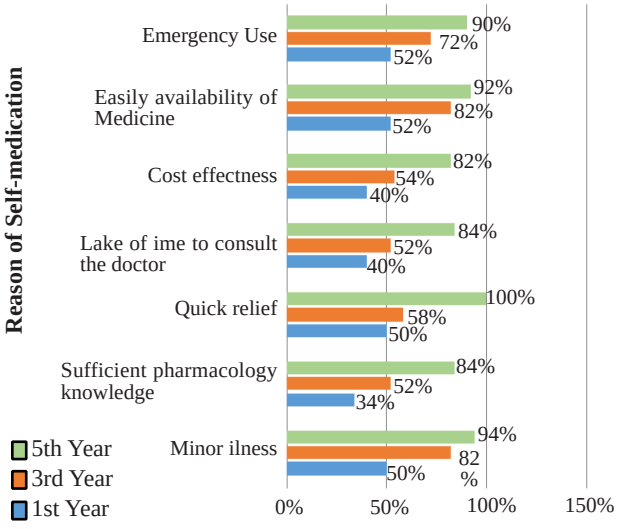
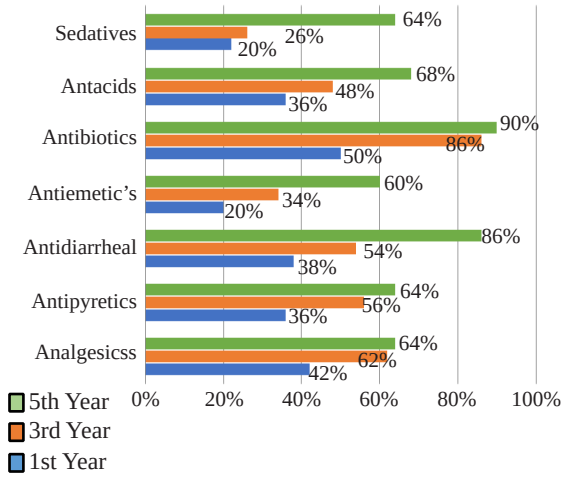


Figure 2: Type of Self-Prescribed Medicines



In comparison with that, the study conducted in 2011 on 1st and 3rd-year medical students noticed no significant difference.[14] In the present study, the most common indication for self-medication noticed in students of 1st, 3rd and 5th years was headache, flu/cough, fever and pain with a p-value of < 0.001. Another study conducted on medical and non-medical students in which the medical students were observed to practice self-medication for bacterial and viral

infections had a p value of 0.001. While the medicines frequently consumed were analgesics, which were about 88.5%, others are antipyretics and vitamins.[10] In contrast with that in the current study, it was noticed that antibiotic consumption was more prevalent in the 5th year students. One of the studies conducted in Nepal noticed that the common utilization of drugs is 31% of antipyretics, 26.2% of antibiotics, 18.89% of analgesics, 10.1% of antihistaminics.[15] While in the current study, the percentage of antipyretics was 36%, 54%, and 64%; antibiotics were 50%, 86%, and 90%, analgesics was 42%, 62%, and 64% in 1st, third and 5th years respectively. According to the study of King Khalid University about the consumption of self-medication among the medical and non-medical students, the results showed that the majority of the medical and non-medical students prescribed self-medication.

The government authorities have to take an initial step to stop this unethical practice and improve awareness among the students. Similarly, in our society by the results of this study, maximum students agreed with their involvement in prescribing self-medication. The only difference was found among the initial level students as compared to other higher level of students.[16] One of the studies was conducted at the University of Gondar (Ethiopia) among the medical and non-medical students to evaluate the perception of self-medication from student's standpoint. The results concluded that the common ratio of students, both medical and non-medical had significantly engaged in self-medication with maximum students involved in prescribing analgesics same as in the present study.[17] Following the study in Iran which was designed to evaluate two different theories related to the Health Belief Model of self-medication and self-therapy among 90 students from medical sciences, the data was collected through test scores. After giving knowledgeable session to the students regarding benefits and hazards related to self-therapy or medication, students got higher scores in post-test analysis and researcher achieved his goal to educate the students about the consequences of self-medication.[18] Malaysian Defense University conducted a study about self-prescribed antibiotics by the students of medical sciences with results similarly showing significant number being involved in prescribing antibiotics as a purpose of self-medication. The ratio was approximately similar among medical and non-medical students. As per the study results of the present study, there is a higher percentage of medical students involved in self-prescribing drugs evenly in respect to students from any level.[19] Research that was conducted among the undergraduate students of pharmacy from Bangladesh about 88% of the total participants were involved in self-prescribing practice. About 83% of students had habit to check the label and 87% surely considered the expiry date. The study concluded higher percentage of undergraduate students involved in self-medication practice specifically in minor cases.[20] The reason might be that the students of 1st year up till now do not go through the details of medications. Meanwhile, it is at a disquieting leap that learning and training of the students is necessary. Still, self-medication is tough to eliminate and the risks of drug interfaces with its adverse effects might upsurge.

It is recommended that through these findings, the medical curriculum should be upgraded to make the students aware regarding the unethical aspect of the self-medication, their consequences. Being a part of community and as health advocates, it is our responsibility to stop this unwanted act of medical or non-medical persons and take a step to eradicate the culture of self-medication from our society.

To address the limitations of the study, there may be an issue of accuracy and respondents may give fake information. Surveyor bias, may ask the question just to stimulate for the desire response. In-depth information may not be elicited and sample may not be a proper representation of the population.

CONCLUSION:

The results from the data concluded that a higher percentage of students were involved in self-medication. In respect to the level of the students, first-year students showed low frequency due to initial stage of studies while their level became upgraded and number of students significantly increased due to knowledge regarding pharmacology and management plan in clinical years.

Author Contribution:
Hina Khan: Conceptulization
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Muhammad Sajid Khan: Drafting of Article
Khalique-ur-Rehman: Conceptulization
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Original Article

Deficiency of Vitamin D: Influence on Diabetic Retinopathy and Hearing Loss Among Patients with Diabetes Mellitus Type 2

Mashhood uz Zafar Farooq, Syed Inamullah, Shama Mashhood, Mahmood Akhter Rana, Muhammad Faisal Fahim

ABSTRACT

Objective: To find a relationship between serum level of vitamin D with diabetic retinopathy and hearing loss in patients with diabetes mellitus type2.

Study design and setting: This cross-sectional study was carried out at Ophthalmology, ENT and family physician Outpatient clinic of Mohsin Consultant Clinic Federal B Area, Karachi from study was April 2019 to December 2019.

Methodology: Total 181 eligible type 2 diabetes mellitus patients. Complete ophthalmological, ENT and physical evaluation was carried out. Retinopathy and hearing status were recorded and were compared to serum 25-OH Vitamin D levels to find any association. SPSS version 23.0 was used to analyze the data.

Results: Mean age of participants were found to be 60.56±7.3 (SD). When diabetic retinopathy status and hearing status was compared, non-proliferative diabetic retinopathy patients with normal hearing were 24(42.1%), with mild hearing 32(56.1%) and only 1(1.8%) with moderate-severe hearing loss was observed with P-value of <0.0001. Retinopathy status was compared with vitamin D levels. Insufficiency was seen in 14(38.9%) non-proliferative diabetic retinopathy, 2(5.6%) proliferative diabetic retinopathy patients and deficiency level was found in 33(32.7%) non-proliferative diabetic retinopathy and 15(14.9%) proliferative diabetic retinopathy patients. Level of vitamin D was compared to DR and HL status. Significantly low level of vitamin D was found with increasing severity of DR and HL with P-value <0.0001.

Conclusions: Low level of vitamin D was associated with the severity of diabetic retinopathy and hearing loss in patients suffering from diabetes mellitus type2.

Key words: Diabetic retinopathy, Diabetes mellitus type 2, Hearing Loss, Vitamin D.

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INTRODUCTION:

Vitamin D deficiency (VDD) has emerged as a global health issue.[1]The deficiency involves almost all regions and all age groups. VDD is found to be more prevalent in Pakistan.[2] The classical effect of vitamin D is regulation of bone remodelling and mineral homeostasis. Additionally, effects of vitamin D on immune modulation, glucose regulation and in developing diabetes mellitus type 2 (DMT2) have also been found.[3] Study results of Palomer X et al and Joergensen C et al. have demonstrated effects of VDD in developing diabetes mellitus (DM) and its microvascular complications.[4-5] The mortality and morbidity secondary to DM has become worldwide public health issue affecting over 300 million people.[6]

In Pakistan, an estimated 7 million of population is having DM and it has been estimated that by the year 2030 this figure will rise to nearly 13.8 million.[7] Diabetic retinopathy (DR) is an important complication in patients suffering from DMT2. Diabetic retinopathy is found to be a leading cause of visual loss and blindness. DR accounts for 12% of all new cases of blindness each year. Different risk factors have been identified for the occurrence of DR in patients of DMT2 including long duration of diabetes, systemic hypertension, hyperlipidemia, obesity and positive family history of diabetes with elevated blood glucose level being the important one.[8-9] Hearing loss (HL) is one more health problem having devastating effect on the social, functional, and psychological well-being of the person thereby reducing the quality of life**.** Beside causing DR, diabetes also affects auditory function. HL is a frequent finding in DMT2 patients with hyperglycaemia as a cause.[10] Insulin is regulator of glucose metabolism and lack of insulin in DM results in poor glucose

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metabolism leading to elevated blood glucose level. Adequate levels of vitamin D are required for effective insulin secretion as demonstrated in studies of Danescu L.G et al., Cavalier E. et al.[11]

Lack of insulin function in diabetes is linked to VDD as shown in animal model of Mathieu C et al.[12] Studies have identified low levels of Vitamin D as an important risk factor in DMT2 for developing DR and HL.[13-15] In view of the important association of low level of vitamin D this study was aimed to find a relationship between serum level of vitamin D with diabetic retinopathy and hearing loss in patients with diabetes mellitus type2.

METHODOLOGY:

This cross-sectional study was carried out at Ophthalmology, ENT and family physician Outpatient clinic of Mohsin Consultant Clinic Federal B Area, Karachi. Duration of study was April 2019 to December 2019.A prior approval was taken from the ethical review committee of the institute. ERC approval letter with reference number CO/RA/14/2019 was issued by the ethical review committee of the institute. Study was conducted in accordance with principles of the Helsinki Declaration of 1975, as revised in 2000. Non-probability convenience sampling technique was used sample size was calculated from online software openepi.com by taking 5% margin of error and 95% confidence interval. Prevalence of diabetes was 26.3% as of second National Diabetes Survey of Pakistan[16], 2016–2017. The sample size was derived to be 181 patients. Patients suffering from DMT2 of either gender attending eye, ENT and family physician outpatient clinic were included. Inclusion criteria were patient having age between 40-70 years, diagnosed to be suffering from DMT2 for the last three years. Exclusion criteria were patients suffering from Type 1 diabetes mellitus, suffering from any other ocular disorder or surgery, limited outdoor activities, suffering from any disorders other than DMT2 that could affect the retinal microvascular structure like renal failure, liver disorders, cancer, tuberculosis, hyper or hypothyroidism, cardiovascular diseases, epilepsy, and behavioural disorders, patients taking medicines that could affect the vitamin D metabolism like antioxidants, calcium, and vitamin D supplements and those suffering from middle and external ear pathology or surgery.

After considering the inclusion and exclusion criteria, a total of 181 patients were enrolled. Visual acuity with Snellen`s chart and detailed ocular examination was performed. Fundus examination was done with slit lamp bimicroscope using 90 D lens and indirect ophthalmoscope. Retinopathy status was recorded. Severity of DR was classified by Early Treatment Diabetic Retinopathy Study (EDTRS) and patients were categorized as having No Retinopathy, Non-proliferative diabetic retinopathy (NPDR) and Proliferative diabetic retinopathy (PDR).[17]

Detailed ENT examination was performed. Pure tone audiometry was used to test hearing threshold in a sound isolated room. Hearing was described according to WHO guidelines as normal with ≤ 25 dB and from 26-40 dB as mild, 41-60 moderate, 61-80 dB severe and >81dB as profound loss.[18] Mean value of the two ears was used. In final analysis, severe and profound hearing loss is grouped as severe visual loss. Detailed physical examination was performed. Blood sample was taken using all aseptic precautions for measuring serum 25(OH)D level. Vitamin D concentration was considered normal with value of 25-OHD = or > 30ng/ml, insufficiency with level 20.1-29.9 ng/ml and deficiency with value < 20ng/ml.[1]

Data was entered and analyzed on SPSS version 23.0. Mean age was reported in mean and standard deviation. Categorical parameters were considered as frequency and percentages. To know the association between Vitamin D, DR and Hearing status Chi-square test or Fischer Exact test was applied. P-value = 0.05 considered to be statistically significant.

RESULTS:

A total of 181 patients were included in this study. Mean age of participants were found to be 60.56±7.3 (SD) with minimum of 40 and maximum of 70 years. Gender distribution showed 16% (n=29) female and 84% (n=152) male patients.

Most of the respondents had duration of diabetes < 5 years (n=85-46.96%), between 5-10 years (n=75-41.43%) and > 10 years (n=21-11.6%) only. Vitamin D insufficiency was seen in 14(38.9%) NPDR patients and 2(5.6%) PDR patients. Deficiency level was found in 33(32.7%) NPDR patients while 15(14.9%) PDR patients. While Vitamin D insufficiency was seen in 12(33.3%) patients with mild HL and 1(2.8%) with moderate & severe HL. Deficiency level was found in 85(84.2%) with mild HL while 4(4.0%) with moderate & severe HL patients. (Table 2). Level of vitamin D was compared to DR and HL status. Significantly low level of vitamin D was found with increasing severity of DR and HL with P-value <0.0001. (Table 3)

Table 1: Comparison of DR and Hearing status

Hearing	DR status			P-value
	No DR (n=106)	NPDR (n=57)	PDR (n=18)	
Normal	49	24	3	0.001
	46.2%	42.1%	16.7%	
Mild	56	32	12	
	52.8%	56.1%	66.7%	
Moderate & Severe	1	1	3	
	0.9%	1.8%	16.7%	

Table 2: Comparison of DR (Diabetes Retinopathy) & Hearing with Vitamins D levels

	Normal > 30ng/ml (n=44)	Insufficiency 20.1-29.9 ng/ml (n=36	Deficiency < 20ng/ml (n=101)	P-value
Diabetic Retinopathy status				
No DR	33	20	53	0.037
	75.0%	55.6%	52.5%	
NPDR	10	14	33	
	22.7%	38.9%	32.7%	
PDR	1	2	15	
	2.3%	5.6%	14.9%	
Hearing				
Normal	41	23	12	0.000
	93.2%	63.9%	11.9%	
Mild	3	12	85	
	6.8%	33.3%	84.2%	
Moderate & Severe	0	1	4	
	0.0%	2.8%	4.0%	

Table 3: Correlation analysis of DR, Hearing and Vitamin D level

Diabetic Retinopathy status	Hearing Status	Normal > 30ng/ml (n=44)	Insufficiency 20.1-29.9 ng/ml (n=36	Deficiency < 20ng/ml (n=101)	P-value
No DR	**Normal**	31	11	7	0.000
		93.9%	55.0%	13.2%	
	Mild	2	8	46	
		6.1%	40.0%	86.8%	
	Moderate & Severe	0	1	0	
		0.0%	5.0%	0.0%	
NPDR	**Normal**	10	12	2	0.000
		100.0%	85.7%	6.1%	
	Mild	0	2	30	
		0.0%	14.3%	90.9%	
	Moderate & Severe	0	0	1	
		0.0%	0.0%	3.0%	
PDR	**Normal**	0	0	3	0.000
		0.0%	0.0%	20.0%	
	Mild	1	2	9	
		100.0%	100.0%	60.0%	
	Moderate & Severe	0	0	3	
		0.0%	0.0%	20.0%	

DISCUSSION:

The results of this study demonstrated a strong correlation between serum vitamin D levels, the degree of DR, and the severity of sensorineural HL with similar results as in study of Bener et al.[15] In our study, there was a relationship of vitamin D level with DR and HL with P value of 0.000. In the study of Bener et al, this relationship had a significance value of <0.001.

When DR status and Hearing status was compared, NPDR with normal hearing patients were 24(42.1%), NPDR with mild HL were observed in 32(56.1%) patients whereas only 1(1.8%) patient was observed with Moderate and severe HL with significant P-value of <0.001. When compared with PDR, 66.7% had mild and 16.7% had moderate-severe HL with P value 0.001 whereas normal hearing was found in only 16.7%.

Vitamin D level was compared to DR and hearing status separately. In patients having normal level of vitamin D,

75% showed no DR while 22.7% had NPDR and 2.3% had PDR. Similarly, in patients with normal serum vitamin D level, 93.2% had normal hearing and 6.8% had NPDR and none was found to have PDR. Low level of vitamin D with insufficiency and deficiency had significance association with worsening DR (P=0.037) and HL ranging from mild-moderate and severe showed P value 0.000.

In our sample, 75.69% (n=137) patients were found to have low levels (insufficiency and deficiency) of vitamin D. While examining the association of vitamin D with status of DR and HL, it was found that 80%(n=12) patients having PDR and HL were having vitamin D level of <20ng/ml. While 93.9%(n=31) had NPDR and HL with deficiency of vitamin D. Similarly, insufficient level of vitamin D were found in all patients having PDR and HL and 14.3%(n=2) were having NPDR and HL. The 86.8%(n=2) patients who were having HL also showed deficiency of vitamin D and 45%(n=9) had vitamin D insufficiency without retinopathy with P value at 0.000.

Effects of diabetes in the form of retinopathy, neuropathy and nephropathy are well established. However, its effect on sensorineural hearing is examined recently and a relationship has been demonstrated between them by Ooley C et al.[10] A relationship between retinopathy status and level of hearing loss has also been found in our study. Our study also examined the relationship of vitamin D with DR and a positive relationship is found as has been described widely in different studies.[4,13] DR and HL appear to have hyperglycemia as an important common risk factor which occurs secondary to disturbances of insulin secretion which is found to be dependent on adequate levels of vitamin D. In animal model of Mathieu C *et al* and further demonstration in the meta-analysis of B-A et al., hyperglycaemia is linked to deficiency of vitamin D that is required for adequate insulin secretion and function.[11-12] The results of our study have identified vitamin D as a factor for causing DR and HL amongst patients of DMT2. It is therefore necessary to treat VDD to preserve vision and hearing. Vitamin D is also identified to inhibit retinal neovascularization as identified by DM[19], thereby opening avenues for further research. Other important variables like hypertension have also been identified to be causing HL and DR. However, some researchers have found no correlation of VDD and DR.[20-21] Therefore, further research with large sample size, is advised to confirm the association of low levels of vitamin D with DR and HL and to find valid strategies to control the menace of diabetes.

CONCLUSION:

Current study suggest that low level of vitamin D is associated with the severity of DR and HL in patients suffering from DMT2. Correction of VDD and effective glycaemic control are important in controlling the visual and hearing complications in patients suffering from DMT2.

Author Contribution:
Mashhood-uz-Zafar Farooq: Concept, synthesis, planning of research, manuscript writing.
Syed Inamullah: Concept, design, data collection, Literature search.
Shama Mashhood: Planning of research, review of study, manuscript writing.
Mahmood Akhter Rana: Data collection, literature search.
Faisal Fahim Siddiqui: Data handling, data analysis, result writeup

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Original Article

Maternal Factors Associated With Low Birth Weight Babies

Shazia Aftab, Paras Golo, Alma Muhammad Iqbal

ABSTRACT

Objective: To determine the obstetric, antenatal, natal and socio-economic factors affecting low birth weight (LBW) babies.

Study design and setting: The cross-sectional study was conducted from February2019 till May2019 at Jinnah Medical College hospital Karachi.

Methodology: The targeted population was 100 mothers who recently delivered their babies and were present in the hospital during postpartum period. Variables included obstetric history, maternal risk factors, socioeconomic status and education of parents. Weight of the neonates was noted by the doctors within 24 hours of birth. Data was analysed on SPSS version 21.

Results: Variables having significant and positive influence on LBW were; age, activity and occupation of mother, age at first pregnancy, no. of pregnancies, maternal anemia. The 48% of low birth weight babies were present in mothers belonging to younger age group (18-20 years). The incidence of low birth weight increases with increased number of pregnancies, women with greater than 3 pregnancies had 18% of 1.6-2kg of weight of babies, 12% of 2.1-2.5kg of weight, 10% of 1.1-1.5kg of weight. Mother's with poor diet had 36% of 2.1-2.5kg of weight. Women with high activity during pregnancy having 53% of 1.6-2kg of weight babies. Regarding occupation 40% of housewife's risks of 1.6-2kg weight of baby with p-value of <0.05 as activity during pregnancy was high.

Conclusion: Factors like younger age women, multi-parity, increased physical activity maternal diet, anemia due to nutritional deficiencywere contributed to low birth weight babies.

Keywords: Antenatal care (ANC), Anemia, Low birth weight babies (LBW), Maternal diet, Perinatal death.

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INTRODUCTION:

Low Birth Weight Babies (LBW) is a multifactorial outcome and remains a public health problem. It is an important predictor of newborn health and survival and is closely associated with fetal and perinatal mortality and morbidity.[1] LBW contributes 60% to 80 % of all neonatal deaths.[2] The World Health Organization (WHO) defined low birth weight (LBW) as birth weight (BW) below 2500gms.[3]

More than 20 million infants worldwide, representing 15.5 percent of all births are born with low birth weight, 95.6 percent of them in developing countries[2],9% in Latin America, and Brazil showed 8.0% [3]. According to data from 111 countries, Yemen has the highest percentage of LBW (32%) and 30% for India and Bangladesh. In contrast to neighboring countries like China and Iran; the prevalence of LBB accounted for (6%) and (7%) respectively.[4]

Pakistan is a developing countries with highest rates of LBW, ranging from 19% in urban areas to 32% in rural areas. It contribute high neonatal mortality which is estimated to be 58 per 1000 live births and high stunting rates in children aged < 5 years such as 44%.[5]

The birth weight is not only related with critical determinant of child survival, growth and development but also it is valuable indicator of maternal issues or risk factors and socio economic valuessuch as residence (urban-rural difference), mother's age and occupation, birth order, the family's income and many maternal conditions such a nutritional status, mother's educational and health status.[6] Studies suggest that short maternal stature, very young age, high parity, close birth spacing were all associated factors.[7]

Low birth weight children may face health complications throughout their lives like atherosclerosis, renal disease, non-insulin dependent diabetes mellitus, asthma, hypertension, obesity, psychological stress, hepatoblastoma, respiratory problems, ophthalmologic complications[4], abnormal cognitive development, neurological impairment

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and poor school performance.[8] Low birth weight is an indicator to calculate the possibility of a child surviving and many researches have been carried out on its causes and its effects. Actually, there is an exponential correlation between low weight, gestational age, and perinatal mortality.[9]

The prevalence of LBW in any population reflects its socio-economic development and it is a good alternative to measure the developmental status of the country[7]and it can also be used as a good indicator of mother's nutritional status. The measure to reduce the incidence of low birth weight becomes most successful during the first year of life as it is most important factor affecting the infant mortality and morbidity. Weight of the newborn is a universal undeniable predictor of healthy infancy and childhood.

The risks of perinatal and infant mortality rates are greater among the low birth weight infants. In addition to increasing risk of mortality, low birth weight is also found to be associated with morbidity and long term developmental problems among those babies who survive.[10] It is also recognized that the known factors for pre-term delivery and fetal growth retardation are associated with LBW such as low maternal food intake and illness, especially infections.[7] It is public health significance that LBW causes mental retardation and high risk of perinatal, infant mortality and morbidity and it is evident that LBW is responsible for high perinatal and infant mortality.[11]

LBW reflects inadequate nutrition and ill health of the mother. There is a strong and significant positive relationship between maternal factors and birth weight of the babies and it is generally assumed that prevention of LBW results in a reduction in perinatal mortality hence the rational of the study was to identify the maternal factors associated with low birth weight.

Therefore aim of our study was to determine the obstetric, antenatal, natal and socio-economic factors affecting low birth weight (LBW) babies.

METHODOLOGY:

This was a cross sectional study for determination of LBW incidences and factors that lead to LBW of neonates at the time of delivery. The research work was conducted from February2019 till May2019 at tertiary care hospital of Jinnah Medical College hospital Karachi. The ethical approval was obtained from the relevant ethical review committee of Jinnah Medical College hospital Karachi (Ref# JMC. ERC.02.0802.19). The records were checked in the NICU of hospital and then questionnaire were being filled by doctor after taking verbal consent from mothers.

The exclusion criteria included babies of normal birth weight. Purposive sampling technique was adopted to reach the specified sample size that was calculated by WHO sample size calculator. A sample size of 100 mothers with their neonates was taken. The targeted populations were women who recently delivered their babies and were present in hospital during postpartum period. Only mothers of live born single babies with birth weight less than 2500 grams LBW (low birth weight) irrespective of gestational age were recorded by the doctors within 24 hours of birth.

All the eligible cases were recruited into the study and data was recovered after interviewing the women, from the patient files, labor ward register and hospital maternal health medical records. The data included maternal and neonatal outcome which includes demographic details, labor and delivery details and immediate postpartum period complications of pregnancy.

The socio-demographic variables such as age, parity, age at first pregnancy, interval between pregnancies, maternal anemia, occupation of mother, diet, activity, antenatal visits, maternal education and occupation of husband and household income, type of delivery i.e. spontaneous vaginal delivery (SVD) and caesarean section and perinatal outcome measured were preterm delivery (<37 completed weeks), low birth weight (= 2.5kg at any gestational age) were assessed. Data were analyzed on SPSS version 21. The data was calculated by chi-square testing. P value < 0.05 was considered as statistically significant.

RESULTS:

Total 100 mothers were assessed and given birth to low weight babies. Assessing the age; 48% of low birth weight babies were present in mothers belonging to younger age group (18-20 years), 50% in >20 years group and only 2% in <40 years age group. Table 1: Depicted the antenatal factors affecting LBW of baby. The incidence of low birth weight increases with increased number of pregnancies, women with greater than 3 pregnancies had 18% of 1.6-2kg of weight of babies, 12% of 2.1-2.5kg of weight, 10% of 1.1-1.5kg of weight, 5% of 0.5-1kg of weight. Women with 2 pregnancies had 10% of 1.6-2kg of weight, 7% of 1.1-1.5kg of weight, 3% of 2.1-2.5kg of weight and women with 1 pregnancy causing 13% of 1.6-2kg.There was statistically significant association was found for diet During Pregnancy causing low weight babies at p value of <0.03. The were 45% mothers gave birth to 1.6-2kg of baby weight and 19% with 2.1-2.5kg weight of babies having average diet during pregnancy.

Women with high activity during pregnancy having 53% of 1.6-2kg of weight babies, 30% of 2.1-2.5kg of weight. Moderate activity during pregnancy causing 33% of 1.6-2kg of weight and 2.1-2.5kg of weight of babies at p-value of < 0.03. Maternal anemia was present in 17% in 1.6-2kg of LBW newborns and 11% in 2.1-2.5kg of LBW newborns p value of <0.05 shows significant association. Association of contraceptive causing low birth weight of babies was found at p value of <0.053. Not using of contraceptives is increasing the risk of low birth weight of baby. From socio-economic status of the enrolled participants; significant

variables were education and occupation of father and household income that contributes p-value of <0.046 and <0.03 respectively.

Table 1**:** Antenatal factors of pregnant mother affecting LBW of Neonates

Antenatal Factors	**%**	**P value** (0.05)*
Age at marriage		
18-20yrs	48	0.03
>20yrs	50	
<40yrs	2	
Parity		
Primipara	13	0.01
Multi-para	87	
Contraceptive use		
Yes	07	0.05
No	86	
Education of mother		
Can sign only	29	0.05
Middle	33	
Higher	38	
*Chi-square		

DISCUSSION:

In this study effort has been made to find out the prevalence and associated factors of low birth weight in the study area and the results helps to determine the causes of low birth weight babies. In our study actors associated with low birth weight of mothers included were maternal age, parity, monthly household income, maternal anemia, diet during pregnancy, maternal occupation, husband occupation, husband education and low socioeconomic status. The role of contraception and birth interval between pregnancies is found to be very important in the study.

In our research low birth weight babies found among mothers having younger age group (18-25 years) and this result is supported by other studies of Joseph Johnson et al[10]and Nirmali Gogoiet al [2]reported that young mothers less than 20 years were related to low birth weight.

There is a significant association of parity & low birth weight found in our study; multigravida mothers had increased risk of low birth weight which is comparable with the study of Radha Kumariet al study[11]that multigravida mother's had more low birth weight babies while primigravida had 2% or less chances of giving birth to low birth weight. While Nayer et al[12] showed significant association of primiparity and low birth weight.

Pregnancy represents a state of increased metabolic requirement, the inadequate intake of key micronutrients may exacerbate the preexisting maternal deficiency, the diet during pregnancy contributed to 90.7% cases of low birth weight babies in literature [13]while it is 60% in our study. Anemia is a common nutritional deficiency disorder and is very common in pregnant women worldwide.[14] Prevalence of anemia in pregnant women in developing countries is higher than in developed countries.[13]

In order to get the nutrients you need, you must eat from a variety of food groups, including fruits and vegetables, breads and grains, protein sources and dairy products. A previous study reported that maternal anemia was associated with fetal anemia and stillbirth and further affected embryo development, leading to LBW.[15] Iron deficiency anemia in pregnancy is a risk factor for preterm delivery and subsequent low birth weight. Maternal anemia is not only responsible for maternal mortality but also associated with preterm birth and the incidence of LBW.[16] In our study maternal anemia was associated with LBW and this result is in harmony with various other studies of Dhaka 2009[17], Joseph and Khan A in 2016. [2, 9 11]

Maternal average monthly income was observed to influence the birth weight (BW) of a newborn as mothers who earn higher incomes had less LBW incidence. In current study household income showed to cause 26% cases of low birth weight babies which is evident from the study of Nepal [18] which showed that 57% cases of low birth weight babies were due to low maternal income. Regarding to maternal occupation the present study demonstrated that pregnant mothers who engaged in jobs delivered more LBW babies ($p<0.05$) than others which is similar to other researches.[19,20]

Socioeconomic status in 90% cases causes low birth weight babies according to other studies[13, 16] but in our research it caused 26%. Comparing the others research with the current one few factors were found not causing low birth weight in babies such as maternal education, supplements during pregnancy and antenatal visits.[13,16]

In the study few factors were found not causing low birth weight in babies such as maternal education, supplements during pregnancy, interval between pregnancies and antenatal visits while mother's education had shown a strong association with low birth weight babies in other studies and the incidence of low birth weight is observed more in mothers who were illiterate than in literate mothers which is also supported by study by Joseph et al.[7]

The incidence of LBW was high in mothers which were not using any type of contraception and was found to be statistically significant similarly in the study women with no birth control have high incidence of LBW which is also observed in other studies.[2,11] There were few limitations encountered during carrying out research like language barrier as to speak to participants in their native language. This is recommended that during antenatal period mothers require proper follow-up visits and taking proper doses of iron supplements during pregnancy. Awareness programs

regarding consequences of teenage pregnancy should be conducted. In our study 86% women were not using contraception so the provision of safe motherhood services and expanding access and improving the quality of family planning services may help in reducing the perinatal deaths and LBW babies.

CONCLUSION:

It was concluded that few factors like younger age women, multi-parity, maternal diet and anemia due to nutritional deficiency were contributed to low birth weight babies.

Author Contribution:
Shazia Aftab: Statistical Analysis & References Writing, Drafting of the article, Results and Final Layout, Review of Manuscript.
Paras Golo: Data Collection, Tabulation of Results, Literature Review
Alma Muhammad Iqbal: Data Interpretation & Preparation, Literature Review

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Original Article

Assessment of Location of Mental Foramen in Mandible Using Cone Beam Computerized Tomography

Shoaib Rahim, Maria Shakoor Abbasi, Ali Waqar Qureshi, Ammarah Afreen, Zarah Afreen, Atikah Saghir

ABSTRACT:

Objective: To determine the mean distance of mental foramen from the base of the mandible and mandibular symphysis in patients reporting to tertiary care center using Cone Beam Computerized Tomography (CBCT).

Study design and setting: Cross-Sectional Study was carried out in the Prosthodontics Department, Foundation University College of Dentistry, Islamabad from March 2019 to August 2019.

Methodology: Total 100 patients between the age of 20-45 years were participated. CBCT investigation was carried out and measurements of mental foramen from the base of the mandible and mandibular symphysis in patients were recorded with the help of measuring tools in the software and noted down on the performa. SPSS version 20 was used analyze the data. P value less than 0.05 was considered as statistically significant. . Frequency and percentages were calculated for variable gender (qualitative). For quantitative variables like age, distance mental foramen from the mandibular Symphysis and inferior border of mandible, mean + SD were calculated. Independent samples t-test was used to compare quantitative variables like distance MF from the mandibular symphysis/midline and inferior border of mandible. P values < 0.05 was considered as statistically significant.

Results: The Mean+SD distance of anterior border of mental foramen from symphysis on left and right side were 24.12+2.835 and 24.88+2.637 and from the lower border of mandible were 11.97+1.359 and 12.00+1.764 respectively.

Conclusion: The mean vertical and horizontal distances calculated in this study can provide a useful guide to dentist to safely place dental implants within the inter-foraminal region in our population.

Keywords; Cone Beam Computerized Tomography, Mandible, Mental Foramen

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INTRODUCTION:

Mental foramen (MF) allows the passage of the terminal branch of inferior alveolar nerve (IAN) which is known as the mental nerve. It supplies sensory innervation to the soft tissues of the buccal vestibule, lower lip, and gingival soft tissue mesial to the first molar in the mandibular arch.[1]The location and emergence of this nerve have been described to vary in individuals.[2] Certain studies have suggested a variation, based on geography, gender and as well as history, in the morphology of the mental foramen and neurovascular bundle is transmitted by it.[3,4]

The area of mandible between the mental foramens is assumed to be a safe area for the insertion of dental implants and is often involved in many other surgical procedures. Therefore, it is essential to appreciate the anatomy of this region to avoid any injury to the neurovascular bundles. Sensory dysfunction occurs when the mental nerve is damaged at foraminal region.[5]The sensory dysfunction in the chin and lower lip region is one of the most inadvertently occurring complications during placement of implant in the anterior mandibular region.[6] Damage to mental nerve causes immense suffering to the affected patient leading to hypoesthesia and anesthesia as well as paresthesia and pain. Sensory discomfort adversely affects the patient's quality of life.[7]

It is therefore necessary to have a clear vision/image of the jaw to prevent these damages, which can be achieved by combination of clinical and anatomical knowledge of

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mandibular structures and with the help of findings obtained from clinical and radiological examination.[8] Thus, revisiting the anatomy of mental foramen with the 3D imaging technique, that is, Cone beam computerized tomography (CBCT), will provide a better image quality/resolution and an accurate representation of the structures with a low radiation dose.[9]

The rationale of our study is to determine the mean location of mental foramina (MF), that is, vertical and horizontal, in our population thus identifying the estimated safe zone implant placement in the inter-foraminal region thereby minimizing the chances of damage to the mental nerve.

METHODOLOGY:

This Cross-sectional study was carried out in the Prosthodontics Department, Foundation University College of Dentistry, Islamabad. The study duration was 06 months (March 2019 to August 2019) and a sample size of 100 patients was selected for this study, calculated with the help of WHO sample size calculator. Ethicle approval was obtained from the concerned institute No WDC/2019/1074. A Non-probability consecutive sampling technique was used for data collection. Inclusion criteria consisted of patients of both male and female gender with age ranging from 20-45 years, patients for whom CBCT has been advised as part of their treatment, patients with no history of mandibular fracture, both partially dentate and completely edentulous patients were selected and patients with no history of tumors, cyst or any other bony deformity in the mandible. Exclusion criteria consisted of patients with a history of tumors, cyst or any other bony deformity involving the anterior portion of the mandible within the region of right and left mandibular 1st molar or presence of any radiolucent lesion in the lower jaw in the same region, patients with any jaw growth deformity, patients with any identifiable syndrome, patients on bisphosphonate therapy, patients with osteoporosis and non-visualization of the mental foramen bilaterally.

Prior approval from Ethical Review board was taken. As a protocol all patients presenting to hospital were examined in dental OPD/ diagnostics department and patients with prosthodontic needs were referred to Prosthodontics department. Those patients who fulfilled the criteria (Exclusion and Inclusion) were selected for the study. Patients in whom CBCT was required where advised the investigation done at any nearest laboratory with the facility of this investigation. Most patients reported 3D radiographic images of the patient which were recorded using Newtom vgi CBCT (Verona, Italy). Measurements of the MF from the mandibular Symphysis and inferior border of the mandible were recorded using a measuring tool in panorex view, cross section (FIGURE-1) and 3D model (FIGURE-2) in the software (NNT viewer) provided with CBCT. The measurements recorded were filled in the Performa for each patient separately.

SPSS version 20 was used to analyze the data. For qualitative and qualitative variables descriptive statistics were calculated as frequency and percentages. For quantitative variable mean +/- SD was calculated like age, distance mental foramen from the mandibular symphysis and inferior border of mandible. Independent sample t-test was used to compare quantitative variables like distance MF from the mandibular Symphysis/midline and inferior border of mandible. P values of > 0.05 was considered significant.

RESULTS:

The number of patients selected for this study was n=100. Out of these 100 patients n=50 (50%) were males and n=50 (50%) were females. The Mean + SD and the frequency of age distribution of the patients have been illustrated in Figure-3. Mean + SD age of male patients was 38.82 + 5.401 and female patients was 33.92 + 6.496. Among n=100 patients, n=17 (17%) were completely edentulous and n=83 (83%) were partially dentate patients.

The Mean + SD distance of the Left Mental Forman (LMF) and Right Mental Foramen (RMF) from the mandibular symphysis/midline of all patients was 24.12+2.835 and 24.88+2.637 respectively. Whereas, mean + SD distance of LMF and RMF from the symphysis/midline in males was 24.45 + 2.29 and 24.76 + 2.47 and in females was 23.79 + 3.27 and 24.99 + 2.82 respectively.

The Mean + SD distance of LMF and RMF from the mandibular lower border in all patients was recorded to be 11.97+1.359 and 12.00+1.764 respectively. The Mean + SD distance of LMF and RMF from the mandibular lower border in males was 12.50 + 1.26 and 12.65 + 1.67 respectively. The Mean + SD distance of LMF and RMF from the mandibular lower border in females was 11.44 + 1.25 and 11.34 + 1.61 respectively.

Paired Sample T-Test was used to determine the difference between the distance on left and right side. Statistically significant difference was found between the distance of LMF and RMF from the symphysis/midline of mandible, with a p value of 0.000. There was no statistically significant difference between the distance of LMF and RMF from the lower border of mandible, with a p value of 0.826.

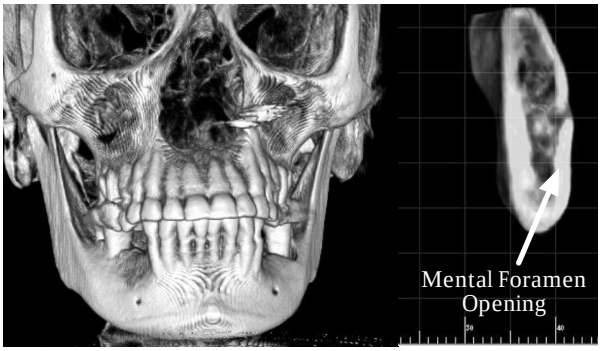
Independent Sample T-Test was used for stratification to determine the difference in distance of the mental foramen between genders. There was no statistically significant difference in the distance of LMF and RMF from the midline between males and females, with p value of 0.244 and 0.665 respectively (Table-1). Whereas statistically significant difference was found in the distance of LMF and RMF from the lower border between males and females, with p value of 0.000 and 0.000 respectively (Table-2).

Independent Sample T-Test was used for stratification to determine the difference in distance of the mental foramen between age groups (divided into 2 groups, that is, Group-

I: 20-32 years and Group-II: 33-45 years). No statistically significant difference was found in the distance of LMF from midline between the age groups with p value of 0.553. Although statistically significant difference was noted in the distance of RMF from the midline between both age groups, with p value of 0.006. Statistically significant difference was found in the distance of LMF from the lower border, with p value of 0.007. Whereas no statistically significant difference was found in the distance of RMF from the lower border, with p value of 0.357.

Figure 1: Cross-Sectional Cut at The Location of Mental Foramen with Measurement Recorded from The Level of Inferior Margin of Mental Foramen To The Base of Mandible with The Help Of Linear Measuring Tool

Figure 2: 3D Model of Patient with Cut Model At The Location of Mental Foramen With Grid Measuring Tool



DISCUSSION:

The precise location of the Mental Foramen (MF) is the most important aspect when considering the placement of dental implants in the anterior mandible, especially in completely edentulous patients where there is an absence of dental landmarks to guide during implant placement. Significant differences have been reported in the location of MF among different ethnic groups. Igbigbi et al. in

Figure 3: Bar Chart Illustrating Frequency of Age Distribution of Patients

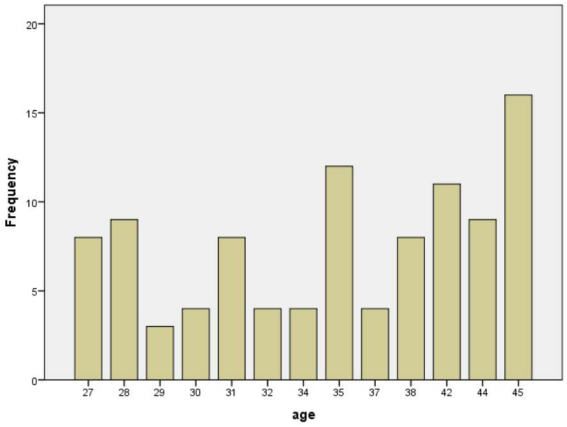


Table 1: Stratification Of Mean Distance Of Mental Foramen On Left And Right Side From The Mandibular Midline With Regards To Gender

Gender	Distance of Left Mental Foramen from Mandibular Midline (mm)		P Value (Independent Sample T-Test)
	n	Mean + SD	
Male	50	24.45 + 2.29	0.244
Female	50	23.79 + 3.27	
Distance of Right Mental Foramen from Mandibular Midline (mm)			
	n	Mean + SD	
Male	50	12.65 + 1.67	0.655
Female	50	11.34 + 1.61	

Table 2: Stratification Of Mean Distance Of Mental Foramen On Left And Right Side From Lower Border Of Mandible With Regards To Gender

Gender	Distance of Left Mental Foramen from Lower border of Mandible (mm)		P Value (Independent Sample T-Test)
	n	Mean + SD	
Male	50	12.50 + 1.26	0.00
Female	50	11.44 + 1.25	
Distance of Right Mental Foramen from Lower border of Mandible (mm)			
	n	Mean + SD	
Male	50	12.65 + 1.67	0.00
Female	50	11.34 + 1.61	

Malawians and Mbajiorgu et al.[10,11] in Zimbabweans mandibles reported that the commonest position for (MF) was along the roots of 2nd premolar tooth followed by between the roots of 1st premolar and 1st molar teeth.[11] However, Santini and colleagues in British and Green in Chinese mandibles observed that the most common position for MF was between the roots of 1st premolar and 2nd premolar teeth followed by along the roots of 2nd premolar tooth.[12,13] In other studies on Kenyan population the most common position of MF was found to be between the roots of 1st premolar and 2nd premolar teeth followed by along the long axis of 1st premolar tooth.[14] In Malay mandibles the most common position was along the roots of 2nd premolar tooth followed by between the roots of 1st premolar and 2nd premolar teeth.[15] In all of the above-mentioned studies the mental foramen on right and left sides were not considered separate from each other rather they were considered as the same. Another drawback or limitation in the above-mentioned studies had in common was that they used teeth to identify the position of the mental foramen relative to them, which therefore is of little if any or no help when it comes to implant therapy in completely edentulous patients. The position of the teeth in itself is variable and not everyone has perfectly aligned teeth thus in cases of malocclusion, this relative positioning would again be of no help.

In our study; measurements from specific hard tissue landmarks were used to determine the position of mental foramen in our population. These landmarks are stable and do not change whether the individual is dentate or edentulous thus giving much more accurate location of mental MF.[16] in our study the landmarks used where distance of anterior border of MF from midline/ symphysis of mandible and distance of lower border of MF from the lower border of the mandible. In a study conducted by Budhiraja and colleagues to determine the position of MF in the North Indian population same landmarks were used.[4] They considered the location of LMF and RMF separately which is in accordance with our study. According to their study Mean+SD distance of anterior border of MF from symphysis on left and right side were 25.29+0.30 and 25.39+0.66 respectively.[4] These measurements are different from that recorded in our population, that is, 24.12+2.835 and 24.88+2.637 on left and right side respectively. In the same way Mean+SD distance of lower border of MF from the lower border of mandible recorded by Budhiraja et al. were 15.40+0.22 and 15.25+0.24 on left and right side respectively.[4] In our study the Mean+SD distance of MF on left and right side from the lower border were 11.97+1.359 and 12.00+1.764 respectively. These measurements along with other studies show that there is difference in the distance/ position of MF based on ethnicity. Thus, ethnic group should be included in the process of recording history of a patient while selection for dental implant in completely edentulous patient in this region.

In another study conducted by Rashid and colleagues it was found that there was statistically significant difference in the vertical position of MF between males and females.[17] In our study no significant difference was found between males and females in the location of MF. In the same study the authors found that there was no statistically significant difference between the distance of MF from the lower border on the left and right side which is in accordance with our study regarding the vertical position of mental foramen. In a study conducted by Singh and colleague on the position of MF there was significant difference in the distance of MF from the symphysis on the left and right side which is in accordance with our study.[18] Rashid and colleagues also found that there is significant difference in the measurement of mental foramen with that of age with a p value of <0.001.[17] This finding is in accordance with our study.

Variation in the site of MF may also be related to diverse feeding habits thus altering the development of mandibule.[19] Erstwhile clinical knowledge of common sites in local populations may be helpful in effective nerve blocks and surgical procedures. Furthermore, age of the person is related with the difference in position of mental foramina. The differences observed among some studies may also be related to the difference in research methodology, such as measurements recorded on skull or use of different skull marks or photographs — inferior margin versus center or anterior margin of MF. [20,21]

One of the limitations in our study was that we did not take into account the variation in the shape of MF. Numerous variations in the shape of mental have been reported in literature.[11-14] These shapes vary in form from round to oval and other variations. The shape of the MF can also have an influence on the dental implant placement in a completely edentulous patient for prosthetic rehabilitation in the region of MF.[7] This position is crucial for dental implant placement in cases where only 2 implants have to be provided for the replacement of missing teeth in the form of implant supported overdenture. If the location of mental foramen is such that it limits the placement of dental implants in this location the design of the prosthesis as well as implant position and dimensions might also need to be changed.[22] Another limitation was that the size of foramen was also not taken into consideration for our study, though it would have had little effect on the results of current study.[14] Lastly the direction of opening of the foramen and any accessory foramina were also not taken into account for our study.[18] Within the limitations of this study, it is concluded that localization of MF in its various positions is vital for dental surgeons to avoid damage to neurovascular bundle. . Variations do exist in the position of mental foramen in different population groups although the mean vertical and horizontal distances calculated in this study can provide a useful guide to dentist to safely place dental implants within the inter-foraminal region in our population. Further studies

on larger population may be required to better estimate the location of mental foramen

CONCLUSION:

The mean vertical and horizontal distances calculated in this study can provide a useful guide to dentist to safely place dental implants within the inter-foraminal region in our population.

Author Contribution:
Shoaib Rahim: Original idea of research, data collection, statistics
Maria Shakoor Abbasi: Statistics, Literature Review
Ali Waqar Qureshi: Statistics, Literature Review
Ammarah Afreen: Data Collection, Literature Review
Zarah Afreen: Data Collection, Literature Review
Atikah Saghir: Literature Review

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Original Article

Ultrasound Employed to Detect Breast Lumps among Symptomatic Patients in Tertiary Care Hospital

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ABSTRACT

Objective: To assess different pathological breast lesions in ultra sound in a subgroup of population.

Study design and setting: It was a cross sectional study conducted at Bolan Medical Complex Hospital Quetta, Pakistan from June 2018 to January 2019.

Methodology: Total 103 patients with breast swelling, pain and discharge were targeted. Gray scale and Doppler Ultrasound of breast followed by FNAC/biopsy of breast lesion was performed. Data presented as mean ± standard deviation for continuous variables and frequency with percentages for categorical variables.

Results: Out of 48 clinically palpable lumps US detected all of 48 lumps and additionally 12 clinically non palpable masses were detected on US examination. Thus, overall sensitivity of ultrasound in detecting breast lumps was 100%. Fibroadenoma of the breast was diagnosed accurately in 80.3% of women. Ultrasound reliably differentiated cystic from solid breast masses (100%). The sensitivity of ultrasound for detecting breast carcinoma was 63.4% with a positive predictive value of 87.5%, a negative predictive value of 99.5% and accuracy of 58.33%. US findings most suggestive of benign lesions were oval or round shape in 88.3%, well defined margin in 84%, absent lobulation in 86.04% and wider than taller ratio in 90.69% of the cases.US findings of most predictive for malignancy were of irregular shape in 81.8%, ill-defined margin in 90.9% and length to height ratio in 63.6% of cases.

Conclusion: Ultrasound is simple, cheap, safe and relatively accessible imaging modality for evaluation of breast pathologies. Due to its high sensitivity in diagnosing benign breast lesions particularly cystic lesions and fibroadenoma unnecessary interventions can be avoided.

Key words: Breast Ultrasound, Breast FNAC/Biopsy, Breast lump, Nipple Discharge

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INTRODUCTION:

Breast cancer is the leading cause of death among women particularly in the developing world. The incidence of breast masses and associated breast cancer is increasing worldwide resulting 1.6 million new cases in 2010 alone possibly due to more frequent practice of imaging as a screening program. Besides, the incidence of breast cancer is expected to rise causing up to 2.1 million new breast cancer cases by the year 2030.[1] By 2020, 70% of the 15 million new annual cancer cases will be in developing countries.[2] Breast cancer cases are in developing countries present in relatively young age, mostly late presentation and aggressive course and carry a very low 5-year survival rate of 39%.[3] Breast cancer is the most common cancer among women in Pakistan (33%) followed by cervical cancer (17%) and ovary (6%). [4]

Triple assessment using physical examination, mammography and percutaneous biopsy are the most important way of diagnosing breast lesions in those who have well established health care system**.** However, mammography is a very expensive way of investigation modality which is not affordable to many developing countries. Besides the cost, psychological trauma & morbidity of biopsies particularly for supposed benign lesions is very high.

Ultrasound (US) plays a pivotal role in the diagnosis of breast lesions as well as adjunct to mammography and MRI particularly in those who have dense breast tissue.[5] Assurance of the technical quality of US equipment should follow

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specific protocols.[6] As a general suggestion, women should be aware that US equipment older than 10 years may not yield state-of-the-art examination results. [7] Of note, although automated three dimensional whole-breast US systems can be used by radiographers for generating three-dimensional US datasets. [8] the interpretation of the images always requires the experience of an expert in handheld breast US to keep false positive and false negative calls as low as possible.[9]

Automated whole breast US, approved by the Food and Drug Administration in 2009, offers the potential for acquiring a volumetric three-dimensional breast dataset with a standardize examination protocol. [10, 11]

In women younger than 30 years of age, pregnant or lactating mothers with a palpable lump, focal breast pain bloody nipple discharge, US is the primary imaging test, with a sensitivity and negative predictive value of nearly 100%.Symptomatic women older than 30 years usually require both US and mammography, and in these patients, the negative predictive value approaches 100%. In symptomatic women aged 30–39 years, the risk of malignancy was 1.9% and the added value of adjunct mammography in addition to US was low.[12]

Mammography is the gold standard investigation modality in breast screening with a detection rate of 85% of the prevalent breast malignancies.[13] However, for screening, US is increasingly being used to detect early breast cancer worldwide. According to a multicenter trial of combined screening with mammography and US (ACRIN 6666), it reported higher cancer detection in high-risk women who underwent annual ultrasound screening in addition to mammography compared to those that underwent mammography alone, the combined screening detected an additional 4.2 cancers per 1000 women.[14]

The use of Color Doppler ultrasound (CDUS) for characterizing breast lesions has increased in recent years. On CDUS malignant lesions were more vascular than benign lesions. Blood vessels were detected in 97.4% of the malignant group and in 35% of the benign group.[15]

Among those < 35 year of age the sensitivity, specifity and positive predictive value of US in diagnosing malignant breast masses was found to be higher compared with those > 35 year of age. In addition, the chances of missing a lesion or indeterminate results were less in those < 35(11.11% vs. 14.29%).[16, 17]

In a setup with lack of resources and unaffordable patients; ultrasound can play a key role as first line of investigation for benign lesions where other modalities like mammography, CT scan and MRI are unavailable and unaffordable and indeed it was the rationale of the study.

Hence, the aim of the study was to assess different pathological breast lesions in ultra sound in a subgroup of population.

METHODOLOGY:

This cross sectional study was conducted at Bolan Medical Complex Hospital for a period of 7 months from June 2018 to January 2019 after approval from ethical review committee and includes 103 patients. The source of population were all women with breast mass, pain and discharge referred to radiology department from inpatient and outpatient care units at Bolan Medical Complex Hospital. Individuals with history of proven malignancy and on treatment, breast surgery or recurrent breast cancer were excluded. Consecutive sampling technique was employed to select samples.

A comprehensive standard breast ultrasound examination was performed on all subjects by the principal investigator using TOSHIBA (XARIO 200) machine. All patients were examined in supine position using a high frequency linear-array transducer (7.5 MHz) that provided adequate penetration and a high resolution image. Scanning of both breasts and axillae were done in different planes. Real time imaging of breast lesions was performed using both gray-scale and color Doppler techniques. The imaging characteristics of a mass (location, size, shape, margins, echogenicity, contents and vascular pattern) were identified. FNAC results were collected from pathology department using their chart number.

All completed questionnaires, ultrasound and pathologic result data checked daily for completeness and consistencies. Then data has been coded and entered into a personal computer using Epi-data version 3.1. Data was cleaned with consistence checks and analyzed using STATA version 14 packages. Tables were used to summarize frequency distributions and percentage of the data. Data presented as mean ± standard deviation for continuous variables and frequency with percentage for categorical variables.

RESULTS:

A total of 103 patients were studied with a mean (±SD) age of 31.1±10.1 (range: 8–60) years. Of the 103 women, 60.19% (62 out of 103) were in the age group of 20-35 followed by 32.04% (33 out of 103) in the age group of 35-50 years. Majority of them were married (77.67) and were Christians (94. 17%). Slight majority (51.46%) lived in rural areas (53 out of 103 candidates). 70.87% (73) of candidates had history of breast feeding (82.19% feed for more than 2 years).

In this study, most of patients had late presentation with a meantime of (±SD) 1.62 ±2.14 yrs (range: 0.19 – 10yrs). Most patients had presented with a complaint of breast lump 53(51.4%) and seven (6%) subjects having breast pain 45(43%) and breast discharge.

On clinical evaluation, mass was detected in 46% (48) of patients, breast size asymmetry in 26 (25.24%) cases and skin thickening in 5(4.85%) of patients. Majority of the masses (70%) were located on the right breast, 28% occurred on left and the rest 2% on both breasts. Of all 48 palpable

masses, US detected all lumps with additional 10 masses not reported on clinical evaluation. Axillary lymph nodes were palpable in only two (1.9%) patients.

On US examination, mass was detected in 58 cases, from these 42.8% were identified on right outer quadrant followed by 25% on left outer quadrant. Total 74.13% of masses appeared as solitary masses but the remaining 24.13% presented as multifocal masses involving either a single quadrant or multiple quadrants. Both breasts were involved in only 4 % of patients.

Calcifications were detected in 13 masses. From these nine (69.23%) were coarse, three (23.08) were punctuate and one (7.69%) rim like calcification. Six (46.15%) of calcifications were seen in benign masses but the other six (46) were seen in malignant lesions. On pathologic correlation, four (66%) coarse and two (33.33%) punctuate calcifications were seen among malignant masses (pr-0.009).

From 58 breast masses evaluated for their shape, 28 (48.2%) had oval shape, 16 (27.5%) had irregular outline and the 14 (24.13) had round shape. Among benign masses the predominant reported shape was oval 27 (62.7%), followed by round 11(25.5%) and five (11.6%) had irregular shape but nine (81.8%) malignant masses showed irregular outline (pr-0.001). Figure 1 show hypoechoic mass with lobulated margins and perifocal fat thickening is suggestive of malignant lesion on ultrasound which was later proven by histopathological findings.

The margins of 58 masses were evaluated. The majority of the masses, 39 (67.2%) had well defined border and 19 (32.7%) had ill-defined margin. Among those evaluated 14(24.13%) had lobulations whereas 10 (17.2%) had > three lobulations and four (6.7%) cases had < three lobulations. In addition, 44 breast masses (91.6%) found to have wider than taller configuration but 11 (18.9%) had taller than wider configuration. None of the masses evaluated had speculation.

On Doppler flow study 7(12.0%) had hyper vascular flow, two (3.4%) hypo vascular and the remaining 49(84.4%) didn't show any color flow. All malignant masses (100%) showed hypervascularity.

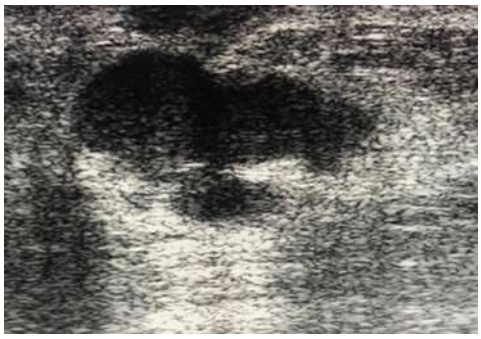
In evaluation of ductal abnormalities on ultrasound, 22 patients had dilated and only one patient had intraductal mass.

Overall 42 patients were reported on US as having normal finding but on pathologic study only 4(9.52%) of them were reported as normal and 37 (90.48%) became benign, one turned out to be suspicious and none diagnosed as malignant. Thus, US have low calculated sensitivity (9.5%) as compared to histopathological study in detecting subtle benign breast lesions. On the contrary US had high sensitivity (92.1%) in predicting grossly visible benign breast lesions. (Graph 1). Eight masses were diagnosed as malignant masses on US study and among these masses 7(87.5%) became malignant and one suspicious. On pathology, totally 11 masses were reported as malignant so the calculated sensitivity of US was 63.4 %, positive predictive value of 87.5 % and accuracy of 58.33%. (Graph 2)

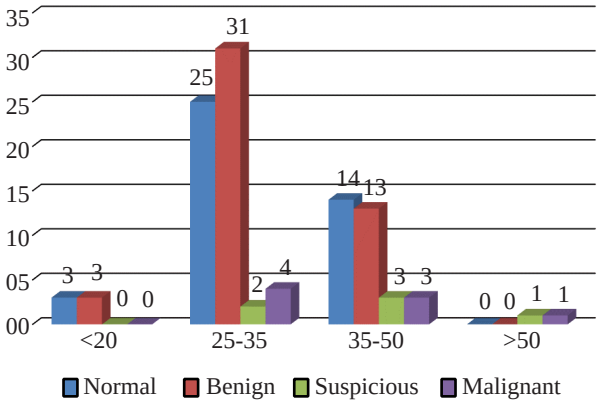
DISCUSSION:

In recent years, breast ultrasound has become an imaging modality of choice in imaging of patients with breast diseases including those who have clinically palpable breast mass or non-specific breast pain even though mammography plays main role in diagnosis and screening of breast lesions. In resource limited countries like Pakistan where mammography

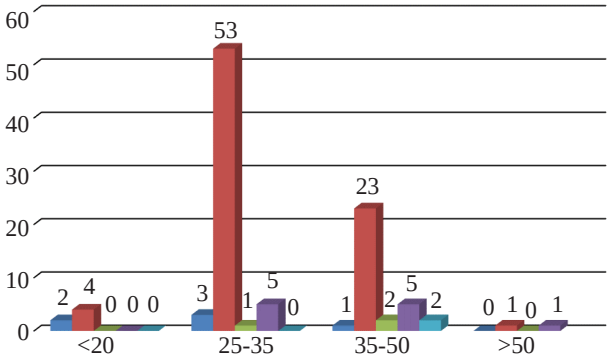
Figure 1: Lobulated hypoechoic mass with perifocal fat thickening



Graph 1: Ultrasound findings in relation to age



Graph 2: Distribution of pathologic findings in relation to age



is not widely available and the availability of high resolution US machines in most of the hospitals, US can play a significant role in diagnosing breast pathologies.

In this study; presence of clinically palpable lumps as the only clinical manifestation alone was seen in 46.6% of patients. This finding is different from the result of Mubuuke et al and Monu et al [18] which showed clinically palpable lumps as the only symptom among 80% of women. The likely explanation for this lower detection of palpable lumps by patients could be due to inadequate awareness in breast self-examination.

Majority of (91.6%) of lumps were detected in the reproductive age group (62.5% between 20-35 years of age and 29.16% between 35-50 years). This result is comparable in a great extent with that of Mubuuke et al (40% between the age of 30-39 years and 20% between 20-29 years) and Kailash et al [19] (44% in the age group between 20-29 years).

US has detected all 48 clinically palpable breasts lumps and additional 10 masses, thus giving 100% sensitivity. This corresponds well with the results of Kailash et al of 95% and Mubuuke et al of 92.5%.

The detection rate of US for cystic lesions in our research was 100% (4 out of 4). This finding is consistent with the findings of Kailash et al of 92%% and Mubuuke et al of 100%. The presence of breast abscess was accurately diagnosed in 85.17% of women. This result is higher than the above researches (both showed a detection rate of 60%).

Overall 42 masses were reported on US as having normal finding but on pathologic study only 4(9.52%) of them were reported as normal and 37 (90.48%) became benign, one turned out to be suspicious and none diagnosed as malignant. Thus, US have low calculated sensitivity (9.5%) as compared to histopathological study in detecting subtle benign breast lesions. The possible explanation for this significant difference between pathology and US could be the subtle benign cellular changes which are reported as benign lesions.

On the contrary US had showed high sensitivity (92.1%) in grossly visible benign breast lesions. Particularly the sensitivity of US in the diagnosis of fibroadenoma was 80.9%. This finding is consistent with the findings of the Kailash et al of 81.6% and slightly better than the result of Mubuuke et al of 75%.

US findings most suggestive of benign lesions were oval or round shape in 88.3% of cases, well defined margin in 84%, absent lobulation in 86.04%, wider than taller ratio in 90.69%. This result was comparable to the findings of Kailash et al which showed oval or round shape in 95%, well defined margin in 86% and wider than taller configuration in 87% of cases. It was also consistent with the findings of Shukla et al [20] which showed oval or round shape in 88.24%, well defined margin 87.1% and wider than taller configuration in 84.38% of the cases.

Most of benign masses (67.4%) had hyperechoic texture followed by heterogeneous in 16.2%, isoechoic in 11.6% and hypoechoic in 4.65% of patients. This result relatively coincides with the result of Shukla et al which showed isoechoic and hyperechoic masses appear benign in 81.2% & 80% of women respectively.

Breast cancer was histologically diagnosed in 11 patients and from these, US correctly diagnosed seven of them as malignant and the other four as suspicious, thus a sensitivity of 63.4%,PPV 87.5 % and accuracy of 58.33% in detecting malignant masses and 100% sensitivity in identifying malignant and potentially malignant breast masses. This diagnostic accuracy was better compared to Kailash et al of 65%sensitivity and higher than Mubuuke et al of 57.1% sensitivity and comparable with Stavros et al [21] who reported 98.4% sensitivity of ultrasound in classifying breast masses as indeterminate or malignant. In another study a sensitivity value of 95%, specificity of 94.10%, positive and negative predictive values of 95.50% and 93.75% were noted.

US findings of most predictive for malignancy were of irregular shape (81.8%), ill-defined margin (90.9%) and length to height ratio (63.6%). This finding was significantly higher than results seen in the study of Kailash et al: irregular shape 53%, non-circumscribed margins 41% and width AP ratio 39% but consistent with the result of Shukla et al that is irregular shape 73.33%, non-circumscribed margins 61.11% and taller than wide ratio in 70.59%.

From the results of this study and other published articles, it was obvious that US plays a significant role in the diagnosis of breast pathologies particularly clinically palpable masses.

Emerging findings like Resistive Index can be utilized in differentiating benign from malignant masses as well as velocity in neovascularity is also another emerging feature which can be applied for better depiction of differentiation.

In our study US showed higher negative predictive value in diagnosing malignancies. Thus, US can be used to reassure women who have no malignant features.

There were few limitations in our study, like this is single centre based study and sample size is small. We need to have large sample size in order to increase sensitivity and specificity for detection of breast pathologies, especially malignancies.

CONCLUSION:

Ultrasound is simple, cheap, safe and relatively accessible imaging modality for evaluation of breast pathologies. Ultrasound should be the first line imaging modality for pregnant and young women for which mammography is not advisable. Due to its high sensitivity in diagnosing benign breast lesions particularly cystic lesions and fibroadenoma unnecessary interventions can be avoided.

Author Contribution:
Ameet Jesrani: Study design and concept, data analysis, data Interpretation, initial and final drafting of manuscript.
Pari Gul: Data collection and questionnaire design
Nida Amin Khan: Initial drafting of manuscript, data interpretation and literature search
Seema Nayab: Critical revision of the manuscript
Fahmida Naheed: Data collection
Rizwana Rehman: Data collection

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Pre and Post Workshop Knowledge Assessment Regarding ECG and Arrhythmia Management in Medical Undergraduates

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ABSTRACT:

Objective: To determine the effectiveness of ECG interpretation workshops as a useful tool in medical education for teaching the integrated cardiovascular module for undergraduate medical students.

Study design and setting: Cross sectional (pre and post workshop quiz) at Jinnah Medical and Dental College over four months from August-November 2019.

Methodology: Total 80 undergraduate medical students participated in the training session. Pre-workshop Quiz was conducted MCQs (single best answer) to determine the prior knowledge of participants on ECG interpretation and action of antiarrhythmic drugs. Interactive lectures were delivered by the cardiology consultant and faculty of pharmacology. Comprehensive hands-on skill session for 12-limb lead and ECG interpretation was organized by the physiology department. Post-Quiz included MCQs (single best answer). Feedback forms were filled at the end of the training and lecture sessions. Paired students T test was used on SPSS 21.

Results: Total Eighty 4th year MBBSÊparticipated in pre-workshop quiz (MCQs) and post MCQs Sixty (75%) students had an unsatisfactory score and only twenty (25%) had satisfactory scores in pre- training Quiz. Post-training and lecture sessions, Quiz (MCQs) scores had significant improvement. Seventy (87%) students had a satisfactory score of which five students were outstanding and only five (6%) scored unsatisfactory. Feedback form filled and the comments were recorded.

Conclusions: It was found by post workshop quiz scores and feedback regarding interdepartmental integrated activity results in a better teaching and learning outcomes. Post workshop Quiz scores indicated the improvement in ECG interpretation and skills.

Keywords: Cardiac arrhythmias, Electrocardiography, Integrated workshop, Pre- workshop, Post-workshop, Quiz.

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INTRODUCTION:

Interactive teaching and learning such as tutorials, problem based learning, case-based sessions, workshops are all small group teaching and have supportive evidence as being useful and effective pedagogy. The formats may vary, but common strategy is that the students interact with the teacher and a large group may be divided into small subgroups. In tutorial session students get the set task to be achieved. In problem based learning the students follow specific process. On the other hand; workshops are planned for the students to gain active experiential learning focused on specific learning. The workshop is a short term teaching and learning which involves variety of learning activities. [1-2]

Electrocardiography (ECG) training in undergraduate and graduate medical students is one of most essential skills in medical practice. The Electrocardiogram (ECG) is an established technique in cardiology for the detection of cardiac diseases in patients. It is the electrical representation of the contractile activity of the heart and can be recorded easily by using surface electrodes on the limbs or chest of the patient. It is one of the most recognized and used signals in the medical practice.[3]Number of drugs are capable of precipitating arrhythmias which include antiarrhythmic,

anti-anginals, antiemetics, gastrointestinal stimulants, antibiotics, anti-malarials, narcotics, antipsychotics, inotropes, digoxin, general anesthetics, bronchodilators, and drugs that cause electrolyte imbalances[4-10]. These training sessions can improve important skills in undergraduate and graduate students[11].

Comprehensive training for interpretation of ECG monitoring is very important for medical and dental graduates.[4] With the help of interdisciplinary experts, cardiologists, ECG experts and pharmacologist we can make the cognitive ability of students regarding diagnosis and treatment of cardiovascular diseases.[6] Most effective training is achieved by utilizing the basic sciences and clinical faculty thereby integrating the course.[7] Changes in ECG of critically ill patient on multiple drug therapy and due to drug-drug interaction is common cause of arrhythmias which can be avoided by proper knowledge and understanding of the pharmacokinetics and pharmacodynamics of drugs capable of producing arrhythmias.[8-11]

In order to have competency- based learning, assessment by multiple choice questions play an important role (Pugh et.al 2019).[12] Peer -review by independent members to make sure either to include or reject altogether [13,14] The goal is to have a diverse team for better knowledge achievements (Eva et al. 2019).[14]Medical curriculum should be including teaching and assessment strategies while planning and conducting courses for medical students. Assessment or pre-workshop quiz can evaluated the prior knowledge of the participants regarding electrocardiograph interpretation "normal" and "emergency" findings. The Pre- Workshop Quiz included 30 MCQs single best answer for each from any four answer options.

Therefore; this study was aimed to determine the effectiveness of ECG interpretation workshops as a useful tool in medical education for teaching the integrated cardiovascular module for undergraduate medical students. Its efficacy was assessed by undertaking a pre and post workshop quiz.

METHODOLOGY:

It was a cross-sectional study design in which purposive sample technique was used. Integrated ECG interpretation work shop was planned over four months from August-November 2019 among Eighty MBBS undergraduate medical students. The ECG interpretation workshop was pre-planned and registration was confirmed for all the 4th year MBBS students and faculty. All the 4th year MBBS students attending the university participated and were included. All those absent were excluded from study. Ethical approval was taken by ERC of Jinnah Medical & Dental College; Protocol #: 000021/20. All the participating students filled a written consent form. Pre-Workshop Quiz (30 single best MCQ) was conducted MCQs (single best answer) to determine the prior knowledge of participants on ECG interpretation and action of antiarrhythmic drugs. Interactive lectures were delivered by the cardiology consultant and the faculty of pharmacology. Comprehensive hands-on training skill session was organized for 12-limb lead and ECG interpretations. The faculty of department of pharmacology planned this integrated workshop with department of Cardiology and Physiology to improve the overall performance of medical students for interpretation of electrocardiogram and knowledge of actions of various groups of antiarrhythmic drugs. Students were provided with notebooks to note down important concepts of ECG.

Consultant cardiologist conducted a comprehensive and interactive lecture on ECG interpretation normal conductive system, rate, rhythm, axis, P -wave, ST- segment morphologies (Myocardial infarction) and QTc interval. Classification and interpretation of cardiac arrhythmias were taught. Images of patients ECG were included for interactive lecture session. Workshop may improve the clinical reasoning skills in the future clinicians. By improving clinical reasoning, the physician is able to diagnose the diseases inpatients having symptoms[15] The training and skills of 12 lead electrocardiogram (ECG) is one of the most essential and useful diagnostic, prognosis and management of patients that should be acquired in medical practitioners. It is highly essential skill to diagnose "common electrocardiographic emergencies" and "uncommon electrocardiographic emergencies" patterns.[16] Pharmacology, of antiarrhythmic drugs is the most volatile. In medical curriculum the drugs for arrythmia, there action and adverse effects is one of the part which has always been the most difficult part to learn and retain by medical students. Due to polypharmacy there are cases of TdP (torse de pointes) caused by drug-drug interactions. [17] Thus the understanding of pharmacology of these drugs is essential for a better patient care.[18] Post-training quiz was conducted with the same protocol as given in pre quiz (MCQs) to assess that sufficient knowledge had been attained by all the participants after the training sessions. Then comparison was done with the post training Quiz scores on a single best answer.[19]

The workshop was planned during cardiovascular module for medical students ECG hands skills. This was a full day workshop, pre-workshop quiz and ECG training lecture and hands in morning session and after a break the afternoon session included arrythmia management lecture sessions and post-workshop Quiz. The ECG interpretation lecture session included identification of normal ECG (intervals, rate and rhythm) and identifying abnormal (ST-elevation, Supraventricular tachycardia, atrial flutter/fibrillation, AV block, TdP (*torse de pontis*). Hands on skills training included; application of all twelve limb leads at particular location, location and color of limb leads, chest leads and interpretation, interpreting normal/abnormal electrocardiogram, for the diagnosis of various cardiovascular diseases (myocardial infarction, atrial and ventricular arrhythmias). Post- training quiz included MCQs (30 single best answer). All the

participants were required to fill the feedback form for lectures and skill sessions at the end of the lectures and workshop. (Fig.1) Paired students T test was used on SPSS 21. P-value > 0.05 was considered a statistically significant.

RESULTS:

Eighty 4th year MBBS undergraduate medical students participated in this study. They were required to take a pre-quiz prepared by the pharmacology and cardiology faculty to judge their prior knowledge regarding the understanding of electrocardiogram interpretation, action of antiarrhythmic drugs and knowledge about management of arrhythmias. Comparison of pre training quiz score with post training quiz score was analyzed by applying paired t-test was significant (table1). Pre training quiz scores of 60 (75%) participants had unsatisfactory score whereas only 20 (25%) had satisfactory score. Post training Quiz 70 (87%) had satisfactory and only 5(6%) had unsatisfactory score. 5 (6%) obtained outstanding scores (table 2). Pre-training hands on skills 60 participants had unsatisfactory knowledge and skills regarding the matching the color and location of limb leads and interpreting the recorded ECG which improved to 100% satisfactory after the hands on training. Feedback significantly showed great positive response included visual/video, audio, handouts, ECG skills, interactive lectures (table 3) as excellent, very good, good and fair. Workshop had improved the understanding of ECG interpretation skills and pharmacology of antiarrhythmic drugs. With some good suggestions to improve were added. During the interactive lectures they recorded all the interpretation on the workbook provided. The ECG interpretation workshop added to cardiovascular course in curriculum facilitated better understanding and skills in medical undergraduates.

Figure 1: Steps of ECG interpretation & Arrhythmia management training session.

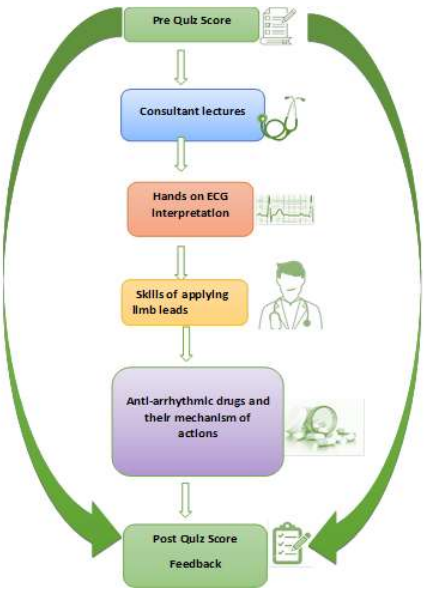

Table 1: Comparison of Pre and Post workshop quiz scores

Total Score (30)	Pre-Work Quiz Scores	Post-Workshop Quiz Scores	*P* value
Range	2- 17	15- 30	0.000
Mean	10.17	19.76	
SD	4.19	4.62	

Table 2: Satisfactory & Unsatisfactory Scores in Pre and Post–workshop quiz

Total Marks (30)	Pre- Training Quiz (No. of Students-80)	Post-training Quiz (No. of Students-80)
0-14 (Unsatisfactory score)	60 (75%)	5 (6%)
15-30 (Satisfactory score)	20 (25%)	70 (87%)
Score 25 -30 (Outstanding score)		5 (6%)

Table 3: Students Feedback and Rating

	Excellent	Very Good	Good	Fair	Poor
Visual	28	25	20	4	0
Acoustics	33	27	20	0	0
Handouts	29	31	20	0	0
Skill Sessions	30	27	20	3	0
Interactive Lectures	34	22	22	2	0

DISCUSSION:

Interdisciplinary collaborative teaching is more effective in improving the cognitive and psychomotor ability of medical students by lectures and hands on skill sessions[6-7]. In the ECG interpretation workshop interdisciplinary teaching was given by cardiology, physiology and pharmacology departments for horizontal and vertical integration. ECG interpretation lecture taken by cardiology consultant, hands on ECG skill session by trained physiology lecturer, explaining students' exact position of limb leads and pharmacology faculty delivered a lecture on action and therapeutic uses of antiarrhythmic drugs for atrial and ventricular arrhythmias. Planning a workshop on ECG interpretation and management of arrhythmias by the faculty of pharmacology and cardiology have tried to create more clear concepts of interpretation of ECG normal and identification of abnormalities like myocardial infarction and arrhythmias which have the most serious outcome and highest morbidity and mortality. [8-11]

The training was conducted by Cardiac consultants, pharmacology professors and ECG limb lead technique by physiology and pharmacology lecturer. Clinical reasoning skills are the requirement of future clinicians, which involve

teaching symptoms of particular diseases, workshops and clinical skill sessions. [12] The undergraduate students were trained to essential skill of interpreting electrocardiographic changes myocardial infarction as being one of most common and life threatening cardiac condition the physician has to deal in everyday practice. Electrocardiograms of patients with STEMI (ST- elevation myocardial infarction) and NON -STEMI myocardial infarction were assessed in interactive lectures and Quiz. As a number of studies have shown very high percentage of senior medical student and interns misinterpreted or missed ST-elevation in patients ECG with acute myocardial infarction.[15] *Thus it is most essential to train i*nterpretation of myocardial infarction in ECG to undergraduate medical students.

It is evident from literature that in interdisciplinary classes, students learned more about cardiac arrhythmias presented by faculty members having extensive experience related to the pharmacology and pharmacotherapy of cardiac arrhythmias.[17-19] Similarly, in our study the interactive lectures on antiarrhythmic integrated lecture sessions were highly appreciated in feedback by medical students in understanding the difficult topic of antiarrhythmic drugs and arrhythmia management.

Outcome of the training workshop was evaluated by pre and post-workshop Quiz which was assessed via multiple-choice questions (MCQs).Ê Pre-workshop unsatisfactory were students who got score below 14 were 60 (75%), satisfactory were 20 (25%). Post – training got satisfactory score were 70(87%) and outstanding scores above 25 were (6%). A study conducted in UK on interactive ECG teaching workshop shown a significant pretest and post test scores.20

It is beneficial to engage students during planning, managing and getting feedback regarding curriculum and other institutional activities to increase their ownership interest and therefore; beneficial for institutions.[21] The feedback from students and the faculty had a mutual-advantage for both the teachers conducting the workshop and those attending. In addition; suggestions and discussions can improve the quality of medical education. As in medical education feedback not only establishes positive learning environment by removing negativity, improves practical knowledge and enhances professional growth. In addition to lecture and skill training sessions, feedback is effective strategy to communicate with students and faculty. It can be obtained by evaluation form or email them to provide comments which will further improve the curriculum.[22-23]

CONCLUSIONS:

It was found by post workshop quiz scores and feedback regarding interdepartmental integrated activity results in a better teaching and learning outcomes. Post work shop Quiz scores indicated the improvement in ECG interpretation and skills.

Author Contribution:
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Knowledge, Attitude and Practices of First Aid Management among School Teachers

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ABSTRACT

Objective: To assess the knowledge, attitude and practices of first aid management among school teachers of Karachi.

Study design and setting: This cross-sectional study was conducted at 4 schools in Karachi, from April to September 2018.

Methodology: School teachers of class 1st to class 8th were included and teachers of coaching centers and academies were excluded. Data was collected through non-probability, convenient sampling technique. Data was obtained using aself-administered closed-ended questionnaire. Data was entered and analyzed using SPSS version 23. Frequencies were calculated. Informed consent was obtained and anonymity of the subjects was maintained.

Results: Total 162 participants aged 20-40 years participated in this study.Among the participants, 84% were females. Participants had inadequate knowledge of first aid and attitude towards first aid management was found to be positive and more than 90% of the respondents were ready to be trained for First Aid management. Data showed unsatisfactory results to manage common childhood injuries at school.Most of participants had poor knowledge regarding the management of epistaxis, choking, fainting and knocked out tooth.

Conclusion: Although the overall attitude of the school teachers regarding first aid practices was favorable, levels of knowledge as well as practice of first aid found to be inadequate and many recognized the need for the introduction of the formal first aid training program at the school level.

Keywords: Attitude, Children, First aid, Knowledge, Practice, Schools.

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INTRODUCTION:

Childhood injuries are an important public health issue that occurs across the globe equally.[1]School students are especially at risk of unintentional injuries which need immediate and appropriate lifesaving management.[2] First aid is initial assistance or treatment given to a person who is injured.[3] It generally consists of a series of simple and sometimes potentially life-saving techniques that an individual can be trained to perform using minimal equipment.[4] According to a survey conducted in Karachi in 2014; based on awareness level of first aid in the general population, 88.8% people in Karachi aged 20-40 years were aware of term first aid.[5] Pakistan is identified as a high-risk country in terms of injury-related mortality for children and adolescents.[6] The overall annual incidence of unintentional injuries was estimated at 45.9 per 1000 per year for Pakistanis, over the age of five years.[7] Unintentional injuries rank third in importance behind cancer and heart disease and are the leading cause of death in children.[4]

School children are vulnerable to a number of risks due to their still maturing physical and mental abilities. During school hours, teachers are first responders in cases of disasters and emergencies.[8] The training also needed to be updated periodically to keep them up with current first aid guidelines.[9]

A healthy safe environment is very important to avoid these hazards besides qualified teachers who can detect any health problem and can give first aid for commonly occurring emergencies in school.[10]

In the light of above evidence, this study was aimed to assess knowledge, attitude and practice among school teachers regarding first aid management.

METHODOLOGY:

This cross-sectional study was conducted from April to September 2018 among school teachers of four schools in

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the region of Defense Housing Authority Karachi. A total of 162 school teachers were selected employing non-probability convenient sampling. Inclusion criteria were school teachers of class 1st to 8th, aged 20-40 years. Exclusion criteria was teachers of coaching centers and academies.A self-administered closed-ended questionnaire was used, comprising of four parts, the first partconsisted of socio-demographic characteristics of participants, the second, third and fourth part included questions regarding knowledge, attitude and practices about first aid, respectively. Informed consent was obtained and anonymity of the subjects was maintained. Data was entered and analyzed using SPSS version 23 and frequencies were calculated. Ethical permission was taken from the ethical review committee of Bahria University Medical and Dental College.

RESULTS:

From the total (n=163) majority of the participants were between the age group 0f 20 – 30 years (89%) and were female (84%).Most respondents had attained tertiary education with Bachelor degree (70%) followed by Masters (60%)Table-1, depicted the demographic characteristics of the participants. Table (2) revealed about knowledge aspect of the study; majority of teachers (96.9%) were aware of first aid knowledge. Most of the teachers (82.7%) knew the common playground injuries of the students. Few teachers (40.7%) knew that a layman could provide the first aid to the injured student if trained successfully. Only about half of them (50%) remembered the emergency number. The attitude of teachers towards first aid management has shown in Table (3) as most of the teachers (93.2%) were interested in learning first aid management and 94.4% of teachers recognized that first aid training should be given to the school teachers. Few teachers (30.2 %) admit their hesitation in giving first aid. Around 98.1% agreed to have a first aid kit in reach all the time, while 91.4% stated that the first aid kit should be cleaned regularly.

Regarding the first aid practice; majority of teachers (95.7%) stated that parents should be informed if the child's condition is not manageable. Almost two-thirds of them (73.5%) provide the correct first aid management of headache while the majority (97%) knew the immediate first aid management when a child gets an attack of asthma. Most teachers (59.3%) aware of the management of First aid of dehydration and 46.9% knew how to manage the limb fracture. Almost one-third of them (29%) knew the management of a child who faints suddenly (Table-4).

DISCUSSION:

Unintentional injuries are the most common cause of morbidity and mortality in children[4] and timely appropriate management can prevent serious outcomes. In Pakistan, nurses are not present in every school, so teachers should be proficient in basic first aid skills. Regarding the knowledge aspect; 82.7% participants had knowledge regarding first aid of common playground injuries and these results are comparable with the study conducted in Turkey and Karachi showed that 81%[11] and 88.5%[12] of people are aware of the importance of first aid respectively.

While addressing attitude; in this study 94.4% agreed that first aid training should be given, 91.4% agreed that first aid kit should be cleaned regularly. These results were comparable with the study conducted in Karachi (2014) and revealed that 90.3% of participants agreed that training

Table 1: Demographic Characteristics of Participants N = 162

Variables		N(%)
Gender	Male	26(16)
	Female	136(84)
Age	20-30	72(44.4)
	30-40	54(33.3)
	40-50	27(16.7)
	50-60	9(5.6)
Marital status	Married	81(50)
	Single	69(42.6)
	Widow	9(5.6)
	Divorced	3(1.9)
Education	Matric	6(3.7)
	Intermediate	26(16)
	Bachelors	70(40.3)
	Masters	60(37.0)

Table 2: Knowledge of Participants Regarding First Aid N=162

Knowledge		Response%
Term First aid	Yes	96.9
	No	3.1
Common playground injuries	Yes	82.7
	No	17.3
A layman should give first aidwithout training	Yes	40.7
	No	59.3
Emergency numbers (115)	Yes	50
	No	50

Table 3: Attitude of Participants N= 162

Variable		Response (%)
Interested in learning first aid	Yes	93.2
	No	6.8
First aid training should be given	Yes	94.4
	No	5.6
First aid kit should be present in school all times	Yes	98.1
	No	1.9
First aid kit should be updated regularly	Yes	91.4
	No	8.6
Would participants hesitate in giving first aid	Yes	30.2
	No	69.8

Table 4: Correct Responses to Study Questions Regarding First Aid Practice

Practice response	Correct Knowledge N(%)
Checking expiry dates on medicines before giving them to children	59(36.4)
Should parents be informed when a child's condition is not manageable?	155(95.7)
First aid for headache	119(73.5)
Immediate management when a child gets an attack of asthma	97(59.9)
First aid of a child has been bitten by a bee/wasp	48(29.6)
First step of treating a bleeding wound	63(38.9)
Immediate treatment of a bruise	60(37)
Immediate action in case of chemical burn after calling ambulance	96(59.3)
Management of a child jamming the finger in a door	96(59.3)
Management after an attack of seizure	61(37.7)
Treatment of an electrical burn	89(54.9)
Management of epistaxis	35(21.6)
Dealing in case of choking	32(19.8)
Manage the bleeding with knocked out tooth	27(16.7)
Management of heat stroke	85(40.1)
First aid for ankle sprain	50(30.9)
Management of Head injury	97(59.9)
First aid of dehydration	96(59.3)
Management of limb fracture	76(46.9)
Fainting	47(29)

should be given in school, 76.2% agreed that regular cleaning of first aid kit should be done.[5]

Regarding practice component; 21.6% of the teachers answered correctly about the management of epistaxis, these findings were lower (66.4%) [13]than the study conducted in Palestine[13] in 2017 and comparable with the study conducted in Egypt where (18%)[14]cases of epistaxis were given correct first aid.In this study 38.9% of the participants answered correctly about the management of bleeding wound,in another study done in India showed that 80.8% people had correctly practiced first aid for bleeding wound.[15]

In this study 29.0% of the teachers correctly answered about the management of a child who faints suddenly and this is comparable with the other studies stated that 18.4% people give correct answers about management of loss of conscious,[11]15.8% cases were correctly managed,[2] respectively. Total 46.9% of teachers answered correctly about the first aid management of limb fracture in our study and this is inconsistent with the another study which stated that 10.5% of school teachers answered correctly.[2] This study revealed that 37.7% of teachers had correct knowledge about managing the child with seizures and these results are much improved than the study of Shanghai, China; which reported that 16.5% of teachers had correct knowledge about managing the child with fits.[16]

Our study showed that 29.6% of teachers knew the correct first aid of treating bee/wasp bite and these results are better than the study of Fiaydali 2018; which showed that 10.3% of participants answered correctly.[11]

Majority of participants (54.9%) knew the correct first aid of electrical burn, while other study in Turkey showed that only 1.8% cases were correctly given first aid of electric burn.[11]In this study, 59.3% of teachers answered correctly about managing the child with a chemical burn, while another study of China showed only 23.05% of participants know the correct first aid.[16] In this study 40.1% of teachers know the correct first aid of heatstroke, other study of China showed that 46.7% of teachers know the correct first aid.[17]Studies have been emphasized that administration of first aid to students soon after injuries can be lifesaving and disability preventing.[16]To keep students safe and healthy, teachers must acquire first aid training.[16] Every school should have standard operating procedures based on school requirements.[15]

The subjective nature of the study was one of the important limitations of the study which increases the chances of response bias. In addition; this study was performed in 4 schools of Karachi,therefore the results cannot be generalized.Also this study assessed knowledge regarding first aid practices only,and not the practical skills.Assessment of practical skills can guide to address the problems faced during practice.

It is strongly recommended to train the school teachers regarding the management of the first aid.

These results showed the importance to train teachers for First aid management and to assure that their skills are updated for practical application.There is a need to establish a compulsory training session for teachers during each academic year.[19,20] First aid kits with all the necessary items must be made available at all times while the students are in the school premises. The government should provide a policy statement on the provision of first aid in all government and private sector schools. In addition;special workshops should be organized in order to teach the basic first aid skills to all the faculty members.

CONCLUSION:

Although the overall attitude of the school teachers regarding first aid practices was favorable, levels of knowledge as well as practice of first aid found to be inadequate and many recognized the need for the introduction of the formal first aid training program at the school level.

Author Contribution:
Tehreem Khalid: Synopsis, sample collection, data entry, discussion, results.
Sana Bashir: Sample collection, data entry, discussion, results.
Farwa Joseph: Synopsis, Questionnaire.
Junaid Abdul Hameed: Synopsis, data collection, data entry
Ali Khan: Synopsis, data collection, data entry
Fareeha Shahid: Data Entry

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Review Article

Potential Neurological Outcomes in COVID-19 Patients: A Review

Abhishek Lal, Mahnoor Khawaja M. Saleem, Yousuf Ali Lakdawala

ABSTRACT:

Coronavirus emerged from Wuhan China, which has been a global challenge for healthcare authorities and individuals. Patients are presenting to the clinicians with neurological symptoms caused by COVID-19 or with preexisting neurological conditions with fear of contracting the virus. We have conducted a literature review on neurological outcomes in COVID-19 patients along with patients with underlying neurological conditions. We searched multiple databases including PubMed, Google Scholar, EBSCO, Semantic Scholar, and Wiley Online for information on neurological manifestations of patients suffering from coronavirus. Clinical data and co-morbidities of the patients were examined. Headache, dizziness, hyposmia, and stroke were among the symptoms reported. Emerging literature is suggesting that coronavirus patients along with respiratory symptoms are also experiencing neurological symptoms. Some medical emergencies such as stroke require immediate treatment to save the patients. Neurologists and clinicians need to recognize these symptoms in order to timely manage and treat the patients.

Keywords: Coronavirus, Manifestations, Neurology

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INTRODUCTION:

From a market in the city of Wuhan, Hubei, China in December 2019 marked the beginning of Novel Coronavirus which was identified from unknown cases of pneumonia.[1] Initially, the viral infection was disseminating in China, leading them to impose precautionary measures to contain and control the virus. However, the virus then started to transmit outside China, and as of now, has engulfed almost all of the countries. Keeping this in mind, on 11th March 2020, the World Health Organisation declared novel coronavirus as a pandemic and guided world health community information on necessary precautionary measures.[2] Additionally, with the rapid dissemination of this pathology, individuals as well as healthcare authorities came under immense pressure and stressed on control and protect oneself and the community. Many studies have suggested that the possible origin of coronavirus is from bats, the virus was transmitted from these bats and then infected mammals.[3] Coronavirus is suggested to infect many organ systems of the body including the central nervous system (CNS), hepatic, cardiovascular, and respiratory.[4] Primary physical effects of Novel coronavirus has been on the respiratory system, but nervous system outcomes have also been seen in patients.[5]

Primarily, the mode of transmission for coronavirus has been through respiratory droplets by a close and direct human to human contact.[6] Furthermore, clinical features of the infected person include fever, dry cough, sore throat, and myalgia, although some patients may also experience neurological and stomach upset symptoms.[7] On one hand, individuals particularly elderly and with underlying co-morbidities are more prone to develop a severe infection as well as mortalities from it.[8] On the other hand, young individuals without any co-morbidities are facing morbidities and mortalities from this virus.[9] A major hurdle in containing this virus is identifying those people who are infected but remain symptomless and are disseminating the pathology around them.

Coronavirus genome has 4 genera consisting of alpha, beta, gamma, and delta, being of single-stranded positive-sense RNA.[10] One of the key topics regarding coronavirus has been its pathogenesis. Previously, many studies have suggested the mode of action of coronavirus in the human body. SARS-CoV after entering the human body initiates its action by binding to Angiotensin-Converting Enzyme 2 (ACE2), which has been suggested to be its primary mode of action.[10] Additionally, SARS-CoV also uses protease TMPRSS2 for S protein priming. In human ACE2 receptor is expressed in tissues like airway epithelium, kidneys, lungs parenchyma, vascular endothelium, and central nervous system.

Some reports have emerged stating the potential of SARS-CoV to invade the central nervous system and mediate its actions.[11] Although damage by this virus has been reported

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in COVID-19 patients with different symptoms arising in them, the extent to which damage occurs is yet to be discovered. Studying the effects of novel coronavirus to CNS can open doorways to patients suffering from their effects, helping in formulating effective treatment modalities.

METHODOLOGY:

For this literature review, we used multiple databases such as PubMed, Google Scholar, EBSCO, Semantic Scholar, and Wiley Online along with the snowballing technique. A large number of articles was found in these databases using the following generic terms such as "Coronavirus", "COVID-19" and "Neurology".

A total of 1508 articles were found. After a discussion with all the authors who performed the literature review, 177 number of articles were screened for relevancy. Articles that were collected were screened based on information extracted from their titles, abstracts, and full text of the articles. The extracted articles were screened by looking at the following information: a) Title, b) Authors, c) Abstract, d) Journal, e) Main text, f) Article type and g) Publication Date. Articles were included on the basis of being related to Coronavirus along with neurological association with it. The exclusion of the articles was mainly due to not being related to the respective literature, not being in English language and articles that were not published in a journal.

Pathogenesis of SARS-CoV in CNS

As it has been mentioned previously, SARS-CoV mainly mediates in action by binding to ACE2 receptors[12]. Central nervous system (CNS) has been found to have these receptors present, thereby, some infected individuals experiencing symptoms related to this organ system.[13] Although some studies do report that the mere presence of these receptors does not necessarily mean that virus is going to invade the particular organ system.[14] Previously, some studies have suggested that some patients with SARS only had the virus present exclusively in neurons.[15]

ACE2 receptors have also found to be present in glial cells and spinal neurons, where they can divide and multiply to damage the cells. Some studies have suggested that the primary mode by which coronavirus invades and damages the CNS is by the way of the olfactory bulb.[16] Through this route, the virus enters the olfactory bulb, and further damages other parts of the brain such as thalamus and brain stem. ACE2 receptors have also been strongly expressed in two areas of the brain responsible for the regulation of respiratory cycle, ventrolateral medulla, and nucleus of the tractus solitaries.[17] Prior studies have suggested that when SARS-CoV invades CNS, it induces direct neural death in the respiratory center of the medulla by upregulation of IL-1, IL-6, and TNF-alpha, thereby initiating inflammatory response.[18] Recently, an emerging hallmark of coronavirus has been coagulopathy, whereby "sepsis-induced coagulopathy" arises in patients being in hypercoagulation state, predisposing to conditions such as stroke.[19]

Neurological damage ensued by COVID-19

Talking about mechanisms by which SARS-CoV causes neurological damage, the virus gains entry into cerebral circulation and sluggishly moves forward. Once within the neuronal tissues, interaction with the ACE2 receptors commences its action.[13] Additionally, because the virus gains entry through the purposed olfactory route, disturbance in smell sensation has been noted in a handful of patients.[20] Moreover, immunological damage to CNS is initiated by cytokine storm whereby novel coronavirus induces innate immune system in the host to release cytokines such as IL-1, IL-6, and TNF-alpha, so producing an inflammatory response which damages the neuronal tissues.[21] Furthermore, all this leads to brain hypoxia, causing further damage.[22] Lastly, pneumonia is caused by the coronavirus, which further aggravates hypoxic brain injury.

Neurological Symptoms of COVID-19 Patients

Literature has stated many potential symptoms experienced by coronavirus patients. COVID-19 patients have neurological symptoms such as headache, myalgia, confusion, and dizziness.[23] Moreover, some patients also experienced hyposmia and dysgeusia as well.[24-26] Mao et al reported that some patients also suffered from cerebrovascular diseases including ischemic stroke and cerebral hemorrhage.[27] Some common neurological manifestations of COVID-19 have been listed in Table 1.

Central Nervous System Manifestations

Location	Manifestations
Central Nervous System	Headache
	Dizziness
	Cerebrovascular Disease
	Epilepsy
	Encephalopathy
	Ataxia
Peripheral Nervous System	Hypogeusia
	Hyposmia
	Neuralgia

1. Stroke:

Stroke has occurred in some coronavirus patients, presenting as a medical emergency.[28] Furthermore, stroke has occurred in coronavirus patients in both young and old age groups.[29] The purposed mechanism that might predispose a person to stroke is by hypercoagulation associated with COVID-19 which induces a sepsis-induced coagulopathy.[19] A study reports that stroke was more commonly associated with COVID-19 patients suffering from a severe infection, which has further contributed in the mortality rates.[30] Additionally, it has been suggested that some individuals who contract

the virus may already have cerebrovascular risk factors such as hypertension, diabetes, hyperlipidemia, and previous history of stroke, predisposing them to stroke when infected with the novel coronavirus.[30] Abnormal laboratory investigations include elevated levels of leukocyte count, C-reactive protein, D-dimer and ferritin levels.[31]

2. Seizures:

Many studies have reported incidents of seizures in patients suffering from coronavirus.[32,33] Initially, the COVID-19 patients presented only with usual symptoms, but later on developed complications such as seizures.[34]

3. Encephalitis:

Initially, the first case of coronavirus patients who suffered from encephalitis was reported from Japan[35]. Physically this patient experienced neck stiffness with Brain CT scan being normal. The mechanism by which SARS-CoV might lead to encephalitis is by direct viral invasion, attachment to ACE2 receptors through the blood-brain barrier.[33] It can be postulated that those patients who suffer from severe coronavirus infection are especially predisposed to suffer from neurological complications.

4. Encephalopathy:

Encephalopathy manifests in patients that suffer from severe COVID-19 infections.[36] Although, it has been suggested that disseminated intravascular coagulation and venous thromboembolism caused by this virus might cause encephalopathy.[37] An elderly patient suffering from COVID-19 has been reported to develop complications of encephalopathy.[38] From China, it has been reported that some patients also experienced hypoxic encephalopathy.[39] Furthermore, cases of acute necrotizing encephalopathy have also been reported in some patients, mechanism of which is mainly by cytokine storm causing a large amount of cytokine to be released and crossing the blood-brain barrier to cause injury.[40] Lastly, those individuals who have been suffering from encephalopathy may have been predisposed to stroke.[41]

5. Dizziness and Headache

Dizziness and headache have been regarded as one of the most common neurological symptoms experienced by COVID-19 patients.[27,42,43] Furthermore, the release of cytokines and chemokines by the macrophages during coronavirus infection might be associated with headache.[44] Although the commonality of these symptoms has been clearly stated, the precise pathophysiology and mechanism are still to be figured out.

Peripheral Nervous System Manifestations:

1. Anosmia and Hypogeusia:

Many studies report that anosmia and hypogeusia are one of the common and first neurological manifestations in coronavirus patients, and may even occur before the occurrence of respiratory symptoms.[34,45] In a study, nearly a quarter of the patient's sample reported experiencing anosmia, with improvement occurring after one week.[46] The virus primarily gains entry into the cerebral circulation by firstly passing through the olfactory bulb. This has been known to cause a disturbance in the smell sensation of the infected people. Studies further report that some patients might only experience disturbance in smell sensation and asked to self-isolate themselves.[45]

2. Skeletal Muscle Injury:

Although less common, skeletal muscle injury has also been on the neurological symptoms experienced by the patients.[47] An elderly person in China, known case of coronavirus, after being admitted to hospital was found to have limb weakness after the neurological examination was performed.[48] Similarly as stated before, skeletal muscle injury is also one of that neurological symptom experienced by patients with severe infection.[49]

Special Care For Patients With Underlying Neurological Conditions

Many patients, particularly those who are above 65 and with underlying medical conditions are more anxious and stressed to contract viruses and might suffer from severe infection. Mortality rates are keenly observed more in this age group. So, emphasis on special care and support for these patients is precisely required.

Multiple Sclerosis: Patients with multiple sclerosis are taking drugs that might predispose them to contract the virus more rapidly and suffer severe infection from it, as compared to a healthy individual. Currently, no consensus has been reached whether to modulate drug therapy for the patient and their susceptibility to contracting the virus.[50] Furthermore, no precise mechanism by which multiple sclerosis patients develop coronavirus infection is yet to be discerned.[51]Recently a study reported adamantanes being successfully used in patients and reported no change in their neurological functions.[52]

Parkinson's Disease: Due to the current situation, the clinical visits required by the Parkinson's Disease (PD) patients are suspended, which increases stress and confusion amongst them. It has been reported that some patients developed increased psychiatric symptoms such as hallucinations, anxiety, and psychosis.[53] Generally, patients have been inquiring about the COVID-19 pathology and their susceptibility to contracting the virus. Currently, no definitive association can be developed between the two pathologies.[54] Additionally, it has been suggested that Parkinson's patients with restricted lung capacity to axial akinesia are predisposed to develop coronavirus infection.[55] Lastly, the correlation between Parkinson's disease and coronavirus is currently unknown, but the subject matter has particularly generated stress among the sufferers of PD.[56]

Epilepsy: Epilepsy, being one of the common neurological disorders, is also highlighted here. Currently, the practice implemented is to keep epilepsy patients out of the hospitals due to the likelihood of contracting the virus and practicing home care.[57] Almost all of the drugs administered to the epileptic patients are not immunosuppressive so decreasing the chances of contracting the virus. Furthermore, it has been stated that patients with epilepsy are not more prone to contract the virus as well as suffering a severe infection from it.[58] Clinicians who are managing epileptic patients should guide their patients on which medications to take.[59]

Neuromuscular Disorders: Patients with neuromuscular disorders are currently on immunosuppressive drugs, increasing their likelihood of contracting the virus. Moreover, patients particularly suffering from Myasthenia Gravis and Lambert-Eaton Syndrome may have respiratory muscle weakness, which may predispose them to develop complications from the novel coronavirus if they contract it.[60] Those on immunosuppressive medicines should be extra-cautious and maintain social distancing more vigilantly.[60] Lastly, it has been stated that Hydroxychloroquine is known to exacerbate symptoms of myasthenia gravis and is, therefore, contraindicated in these patients.

CONCLUSION:

Currently, the entire global community is in grips of the novel coronavirus. However, understanding the neurological manifestations of coronavirus is being evolved rapidly, practitioners should look for these symptoms for timely management of the patients. Timely and early detection not only decreases morbidities but also promotes hassle-free recovery of the patients. Furthermore, additional knowledge on lab work, pathophysiology, and treatment options for these patients should be looked for so that better recovery of the patients can be expected. Knowledge of all these things will help neurologists, scientists, and clinicians to treat their patients optimally.

Author Contribution:
Abhishek Lal: Literature review, drafted the manuscript and formulated methodology
Mahnoor Khawaja M. Saleem: Literature review and dra fted the manuscript
Yousuf Ali Lakdawala: Conducted the final revision of the manuscript

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Review Article

Epistemology of Probiotics

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ABSTRACT

Probiotics are essential in human physiology. They play a vital role in providing immunity, producing Vitamin K, relieving lactose intolerance and shortening diarrhea. Besides; it promises the management of Atopy and other incurable conditions. Not only for humans but probiotics are also beneficial for other species including marine and cattle due to the Ecophysiological responses. Unfortunately, probiotics are much neglected by the wide use of antibiotics and other drugs which not only disturbs but kills them completely. As a result; an individual is more vulnerable to a wide range of critical conditions that could have been avoided otherwise. These potential benefits of probiotics require much attention of the healthy consumer while in the main market for over the counter remedies. To prove these effects in treating and preventing particular diseases and increase the acceptance of probiotics by the general population more clinical studies should be conducted in this area.

Keywords: Health Effects, Immune modulation, Innate Immunity, Micro-biome, Normal flora, Probiotics.

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INTRODUCTION:

The intestinal flora of human body is altered, modified, and reinstated with help of the Probiotics that help in maintaining the homeostasis in the intestinal environment. In past few decades, various researches have been conducted on probiotics. The common probiotic strains are Bifidobacterium, Lactobacilli, S. boulardii, B. coagulans. When these Probiotics are fed along with the Prebiotic, for example, fructooligosaccharide (FOS), Galacto-oligosaccharides (GOS), Xylooligosaccharides (XOS), Inulin; fructans, are termed as synbiotics, which produce various physiological functions in the human body.[1]

METHODOLOGY:

The present study was reviewed from January to March 2020 by using the search engine "Pubmed and science finder". The keywords that were used to gather the information were probiotics, micro-biome, innate immunity, normal flora, health effects, and immune modulation. The large gap was present that focus on epistemology of probiotics from in previous years. Therefore, the emphasis of the review was to gather the previous researches that are especially conducted between 2015 and 2020. The highlighted points that address the detailed epistemology of probiotics in this review are etymology, intestinal microflora, contribution to resistance, causes of induced changes in intestinal flora, indications, adverse effects, and scientific guidelines for testing.

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Literature review

Etymology: According to literature review, it is said to be a full Greek etymology but it is widely considered as a combination of two Latin words of "Pro" meaning "For" and Greek adjective "biôtikos" which means "fit for life or lively". It is also considered to be derived from the word "Bios" which means "Life".[2]

Definition: Probiotics were previously defined as "A substance produced by one Protozoan which stimulated another" by Lilly and Stillwell in1965. Later various modifications were made and it was considered as 'A live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance'. The revision of the definition cleared the confusion caused by the word 'substance' and emphasized 'Live cells' to be the important component of Probiotics [3]

WHO defined Probiotics in 2001 as microorganisms when administered in adequate amounts is confered a health benefit on the host. "Although this definition was widely accepted all around the world, but the European Food Safety Authority had reservations due to lack of measurability of health claims embedded by the probiotics.

The following year, in Oct 2002 they along with FAO (Food and Agriculture Organization gave the guidelines for the Evaluation of Probiotics in Food. Globally efforts were made in 2010 for the first time when academic expert scientists along with representatives from the industrial

world evaluated and recommended for the use of probiotics.

History: The first instance of use of probiotics can be traced to the Greeks and the Romans who used cheese and fermented products. Dairy food fermentations represent the first techniques for food preservation. The idea of colonizing the gut with beneficial bacteria was first given by in the early 20th century.[3] Research studies, manufacturers and consumers began giving their renewed attention to Probiotics in the 21st century.

In 1907, the first hypothesis was given by the along with a Russian scientist. They postulated that certain bacteria can play a positive role that would modify the normal flora in the intestines and replace them with useful microbes.

Metchnikoff gave the postulate which stated that the process of aging to be associated with the putrefactive or the proteolytic bacteria which produces toxic substances in the large bowl. [4] Clostridia, which resides in the intestinal lining, produces , , and with the breakdown of proteins. All these substances are toxic. He mentioned these compounds to be playing key role in "intestinal autointoxication" which with time results in the deteriorative effects of old age. The fermentation of lactose caused by the lactic acid bacteria results in lower pH by the fermented milk which resulted in inhibition of growth of proteolytic bacteria. Henry Tissier was the first to isolate from the breastfed infants. It was named Bacillus bifiduscommunis and later renamed to Bifidobacterium. He came across the use of bifidobacteria and its clinical benefits of treating infant diarrhea. Alfred Nissle in 1917 isolated a strain of E. coli from the feces of a disease-free soldier during the outbreak of Shigellosis. At that time antibiotics were not yet discovered and the management of crisis caused by Shigellosis had to be managed otherwise. He used the strains of E. coli in cases of acute infectious shigellosis and salmonellosis. Rettger and Cheplin, in 1920 conducted experimental studies in rats and human volunteers. In his study, the subjects were fed with , which showed elimination of the pathogenic bacteria like along with other gas-producing bacteria.[4]

Composition: Most of the probiotics available over the counter are composed of Lactobacilli along with Streptococci. It is also seen that Lactobacilli decreases the growth of E.Coli. Few of them also contain bifidobacteria. They may be containing a single strain of bacteria or multiple ranging from 2 to 8 strains in a single preparation. L. bulgaricus, L. acidophilus, L. casei, L. helveticus, L. lactis, L. salivarius, L. plantarum, Streptococcus thermophilus, Enterococcus faecium, Ent.faecalis, BiJidobacterium spp. and E. coli are the most common species used in currently available probiotics. These are all intestinal strains of bacteria except L. bulgaricus and Strep. thermophilus, which are used to produced yogurt. It is regarded as the safest source of probiotic available.[5]

Sources: Probiotics are commonly available as fermented dairy products, other fermented foods or probiotic fortified foods. Sources of these fermented products which contain Lactic Acid Bacteria, which is one of the important Probiotic are the pickled vegetables, kimchi, paocai and sauerkraut, Temph, miso, and soy sauce are the soy products rich in Probiotics whereas yogurt, kefir and buttermilk are the dairy ones. Sauerkraut which an Eastern and Central Asian dish in which raw cabbage is finely cut and has been fermented by lactic acid bacteria. The probiotic bacteria found in it includes , Lactobacillus plantarum, Pediococcuspentosaceus, Lactobacillus brevis, Leuconostoccitreum, Leuconostocargentinum, Lactobacillus coryniformis, and Weissella spp.[6] Kimchi, a Korean traditional dish comprising of salted and fermented vegetables including cabbage, radish, mixed with a wide variety of spices, including gochugaru, spring onions, garlic, ginger, and jeotgal. They contain the strains of Leuconostoc spp., Weissella spp., and Lactobacillus spp. Paocai is found in Sichuan cuisine, in China which comprises pickled cabbage, mustard stems, long beans, peppers, daikon, carrots and ginger. It contains L. pentosus,?L. plantarum,?Leuconostocmesenteroides, L. brevis, L. lactis, and L. fermentum. Kefir is originated from North Caucasus. It is taken from kefir grains which is a type of mesophilic symbiotic culture. It appears like fermented milk drink, like thin yogurt. They contain , , , subsp. bulgaricus, Lactobacillus helveticus, Lactobacillus kefiranofaciens, Lactococcuslactis, and Leuconostocspecies. Buttermilk is simple the fermented dairy milk. It is the liquid left after the churning of butter or cultured cream out of the milk. These days buttermilk is also cultured and it contains either or L. bulgaricus. Other sources include which comprises of along with sp., Acetobacterpasteurianus, A. aceti, and Gluconobacteroxydans.

Administration: There are various methods of administrating probiotics in human body depending upon the condition. They can be added in our daily meals or made into capsules, tablets, pastes, granules, or powder which can be taken directly.[7]

Consumption: Approximately, 41 billion USD were estimated to be the global retail market value for Probiotics in 2015. It included fermented milk products and yogurt which almost accounted for more than half of the total consumption.[8] The innovations in the probiotics mainly from supplements produced almost 4 billion USD which was projected to grow 37% globally in 2020. It was seen in China in 2014 to be rising every year by 20%.[8]

Mode of Action: There are two main mechanisms by which probiotics produce beneficial effects. Firstly, by producing a direct antagonizing effect against the pathogenic bacteria which results in decrease in their number. Secondly, by producing an immunomodulatory effect on the human body with their metabolism directly or by the stimulation of immune response of the body. These mechanisms are well supported by the experimental data.[9] Probiotics also produce

antibacterial substances that cause suppression of the pathogenic bacteria. These antibacterial substances include primary metabolites like hydrogen peroxide and organic acids. Other antibacterial substances with high molecular weight are seen to be produced by lactic acid bacteria but the inhibitory effects accounted are due to the low pH caused and the primary metabolites. Unfortunately, both of them are not active in intestine.[10] Competitive inhibition of the adhesion sites is the other mechanism that plays a vital role in eliminating the pathogenic bacteria from the epithelial lining of the intestines. Probiotics also produce useful enzymes like 8-galactosidase which is useful in conditions like lactose intolerance. The intestines of individuals with normal flora are seen to have more phagocytic activity and production of immunoglobulin when compared with a sterile gut. Ingestion of yogurt has shown increased levels of immunoglobulins when fed to germ-free mice.[11] Tumor growth is also seen to be affected by the lactobacilli showing promising results for their role in cancer prevention. Although to date there is no clinical evidence of it and further studies are required to be carried out in this regard.

Intestinal Microflora and its contribution to resistance

The micro-organisms are acquired by the human body, the moment it passes through the vagina, leaving the sterile in utero environment. This introduction of micro-organisms in the human body leads to rapid increase in their number with time and it stabilizes as a very complex collection of around 1014 micro-organisms comprising 400 different types of bacteria. [12] Various interrelationships forms between these different microorganisms and the host. They are not only subjected to the antimicrobial chemicals produced by the host cells but also the mechanical effects of peristalsis which flushes out the micro-organism along with the food. This is combated by the micro-organisms either by immobilizing and adhering themselves on the intestinal wall or by replicating at a rate more than the rate of elimination.[13]They help in preventing the invasion of pathogenic bacteria by adhering themselves to the sites and blocking the receptors. This protective effect of micro-organisms in the intestines is proven by the fact that the germ-free animals are more prone to diseases that are otherwise not seen in their corresponding conventional animals with the intestinal flora.[14]

Causes of induced changes in Intestinal Flora:

This stabilized gut flora gets disturbed due to some dietary and environmental factors which include excessive hygienic measures antibiotic therapies and stress. The most common condition arising due to lack of normal flora is diarrhea which results due to extensive antibiotic treatment. Administration of oral antibiotics also causes pseudomembranous colitis and Candida infections. Stress also triggers the disruption in the replication of gut flora. It results in decrease lactobacilli and increase in coliforms. It most commonly results from abrupt changes in the emotional or physical environment of a person. Production of cortisol along with other hormonal changes affects the mucous production which results in reduction of gut flora associated with it. Stress most commonly results from abrupt changes in the emotional or physical environment of a person. Production of cortisol along with other hormonal changes affects the mucous production which results in reduction of gut flora associated with it. Space travelers also experience changes in their flora resulting in diarrhea like conditions. All these conditions can be managed by giving the Probiotics. Hence, it has much potential value as all these conditions are seen to be resolved once the gut flora is restored.

Indications

Antibiotic-associated diarrhea

Children are most prone to infections for which wide range of antibiotics are administered to them regularly. During this frequent administration of antibiotics among children, approximately 11% to 40% develop antibiotic-associated diarrhea.[15] When there is imbalance in the intestinal normal flora resulting due to administration of antibiotics, it results in Antibiotic-associated diarrhea. This results in osmotic diarrhea caused by less absorption of short-chain fatty acid due to disturbance in the carbohydrate metabolism. According to, a review conducted in the year 2015, some protective effects were observed in children having antibiotic-associated diarrhea with the use of probiotics. It also showed reducing the occurrence of Clostridium difficiledisease. Several meta-analyses showed positive results for probiotic treatment to be effective in reducing the occurrence, severity and disease progression in Antibiotic-associated diarrhea. Along with reduction in Antibiotic-associated diarrhea, improved stool consistency while on antibiotics and better immune response after vaccinations are with probiotic formulations containing L. rhamnosus was also observed.[16] Probiotic strains used and their dosage is responsible for the efficacy of the probiotic preparations in treating Antibiotic-associated diarrhea. A study showed use of 5 to 40 billion colony forming units/day of L. rhamnosus or in children for the management of Antibiotic-associated diarrhea. This shows that the adverse effects associated with the probiotics can be rare whereas same study states its adverse effects being much when used in debilitated or immune-compromised children.[17]

Immune modulation: Probiotics prevent invasion of pathogenic bacteria with help of competitive inhibition. They also aid the production of IgA by the plasma cells and enhances the process of phagocytosis. It also causes an increase in the proportion of T lymphocytes and the natural killer cells.[18]

Bacterial vaginosis: In case of bacterial vaginosis, probiotic treatment is the application or ingestion of bacteria that are otherwise found in healthy vagina. This helps in curing the infection at a much faster rate.[19] The vaginal flora in healthy

females is 70% Lactobacillus which inhibits the invasion of pathogenic bacteria.

Hypertension: Very limited data is present giving evidence of direct link between hypertension and the use of probiotics. Further studies are required to be carried out to support the data.[20]

Dermatitis: Data supporting the effect of probiotics in conditions like dermatitis is also inconsistent and the American Academy of Dermatology state that the use of probiotics due to lack of evidence to be not recommended in patients of Atopic dermatitis.[21]

Helicobacter pylori: Peptic ulcer caused by Helicobacter pylori is seen to be prevented with the use of lactic acid bacteria in combination with medical treatment. Further studies are required in this regard for the establishment of standard in medical practice.[22]

Intestinal infections: Normal flora present in the gut is observed to be active against E. coli, Campylobacter fetus subsp. jejuni, Clostridium perfringens, Cl. botulinurn, and Yersinia enterocolitica.[23] The particular bacteria which causes this decrease in the pathogenic bacterial growth are yet to be identified.[24]

Lactose intolerance: Lactose intolerance is found commonly all around the world. It results from deficiency of an enzyme p-galactosidase which causes inability to breakdown lactose. Such people are seen to be able to digest lactose when given yogurt as compared to in milk which is confirmed by the Hydrogen breath analysis.[25]

Constipation: Lactobacili also plays an important role in relieving constipation. Acidophilus milk has given significant results as a treatment option for constipation as seen in patients fed with supplements of L.acidophilus having better bowel functions.[26]

Tumors: Lactobacilli produces antitumor or anti-carcinogenic effects by inhibiting the tumor cells directly or by suppressing the growth of bacteria causing production of enzymes responsible for the production of carcinogens from innocuous compounds. These enzymes include p-glucosidase, 8-glucuronidase and azoreductase.[27] They are also found to be responsible for the destruction of nitrosamines which are potent carcinogens and suppression of its precursor nitroreductase.

Hypercholesteremia: Intake of yogurt was seen to have lowering effects on blood cholesterol. These effects were due to the presence of bacterial metabolites resulting in inhibition of cholesterol synthesis in the human body. Some lactobacilli are seen to have direct effect on cholesterol levels by assimilation and elimination from the growth medium.[28] A study conducted in 2002, concluded through a meta-analysis of five double-blinded clinical trials, states that it was observed that the use of yogurt having probiotic strains had an effect on total cholesterol levels with a decrease of 8.5Êmg/dl (0.22Êmmol/l) (4% decrease) and an decrease in serum LDL concentration of 7.7Êmg/dl (0.2Êmmol/l) (5% decrease).[29]

Allergies: People having milk allergy are indicated to have probiotics. Although there is no much data to support the statement. It was seen in a study conducted in 2015 that probiotics when given to infants with eczema, or the infants whose mother underwent probiotic therapy during their pregnancy and breastfeeding stage had less likelihood of developing eczema.[30]

Respiratory Tract Infection: A decrease in the incidence of RTIs was observed in reviews reported in adults.[31]

Inflammatory bowel disease

Standard medication along with the administration of probiotics is seen to be effective in the management of ulcerative colitis but no role was observed in cases of Crohn's disease.[32]

Recurrent abdominal pain: According to a study conducted in 2017, it was suggested that the use of probiotics helps in relieving abdominal pain in short term in children. Proper strains and dosage causing these effects are yet to be worked on.[33]

Asthma: Quality of research is low in this area as well, but literature review does give us some studies showing evidence of probiotic supplementation to be helpful with childhood asthma[34]

Dental Caries: Decrease in the dental caries index was seen as a result of a large study conducted on children.

Adverse effects: On some occasions, bacterial-host interactions are observed after administration of Probiotics. Regardless of this fact, generally probiotics are considered safe, except for few concerns. The conditions which make certain people more likely of having adverse effects include, immunodeficiency, short bowel syndrome, central venous catheters, cardiac valve disease, and premature infants.[35] There exist an evident risk in cases of severe inflammatory bowel disease, which may allow the passage of viable bacteria from the intestinal lining to the internal organs with the blood vessels, and give rise to bacteremia which may further cause adverse consequences.[36] This may also be observed in certain cases of children with low immunity. It can lead to sepsis and can prove fatal. Obesity is also liked with Lactobacillus spp. but it does not have enough evidence to establish any certain relationship.

Scientific guidelines for testing: During administration, the probiotics should be alive. The viability and reproducibility at the time of administration are the main concerns according to the literature review, along with the viability and stability during the shelf life and after once being administered in the stomach and intestinal environments.[37]At the genus, specie and strain levels, they should be taxonomically defined microbes or combinations

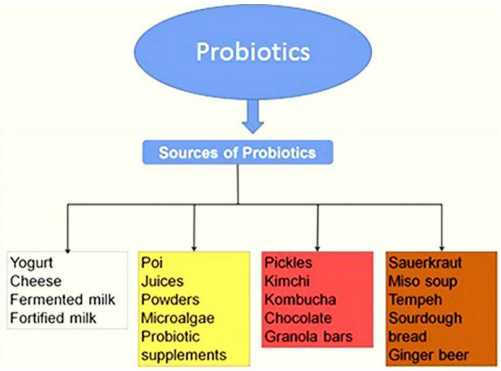
of microbes which requires very precise strain identification.[38] They should be biocompatible and safe for administration.[39]

FAO and WHO have given guidelines[40] which recommends that bacterial strains which may generally be recognized as safe (GRAS) should be evaluated for their safety as a potential probiotic with help of minimum required test:

- Should belong to a strain of bacteria capable of producing beneficial effects in the human body.
- Should be safe, non-toxic, and non-pathogenic.
- Should not have any adverse effects.
- Should be found as viable cells, so effective dosage can be given.
- Should be able to survive, metabolize and reproduce in the gut environment.
- Should be able to be stored for long periods under storage and field conditions.
- Antibiotic resistance patterns should be determined.
- Should be assessed of metabolic activities.
- Epidemiological surveillance of adverse incidents should be carried out in consumers.

Scope of Research: Regardless of the beneficial effects, the clinical use of probiotics is its early stages. Further studies and clinical trials are much required to establish evidence. Although being popular in most parts of the world, the scientific data does not exactly prove any cause and effect relationship. They are still subject to preliminary research for the evaluation of their physiological effects in the human body according to the European Food Safety Authority. It is believed that the beneficial effects of Probiotics are due to long-term healthy dietary changes. Although it remains controversial it is also proposed by the use of probiotics mainly the lactobacilli to be playing role in obesity. A controlled evaluation should be carried out for the documentation of its health benefits. Products which comprises of live organisms that may reproduce in the intestines should be considered only.

Figure 1: Foods rich with probiotics



CONCLUSION:

Probiotics are non-pathogenic micro-organisms which are administered to improve the microbial balance in the human body. They produce their physiological effects through various mechanisms, which may include, change in pH-causing more acidity, decreasing invasion of pathogenic bacteria by competitive inhibition and immune modulation. Dosage and the type of bacterial strain to be used need to be established by conducting clinical trials.

Author Contribution:
Aafaq Khan: Conceptualization and Reviewing
Naveed Faraz: Literature survey
Faisal Hanif: Writing-original draft preparation
Mahparah Mumtaz: Editing and reviewing

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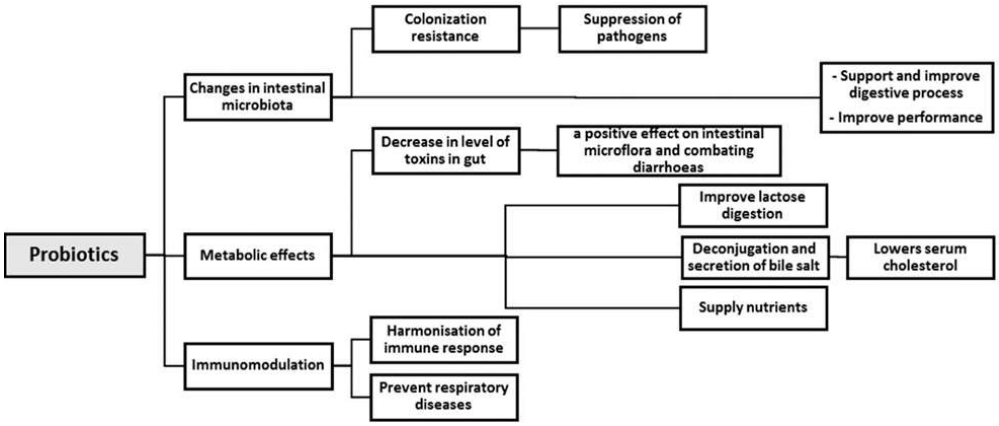
Figure 2: Metabolic effects of Probiotics



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Case Report

Transient Global Amnesia as a Presentation of Frontal Lobe Meningioma – A Case Report

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ABSTRACT

Meningiomas are amongst the most common primary brain tumors, accounting for around one third of cases. They usually present with focal neurological deficits, signs of raised intracranial pressure or seizures. Transient global amnesia (TGA) is an uncommon disorder, usually linked with severe emotional or physical stress, migraine variant or vascular risk factors. It is believed to originate from hippocampal dysfunction. We present the case of a 65 year female, who visited our hospital with two episodes of transient amnesia. Both episodes lasted for 4-5 hours with no other focal neurological dysfunction noted. She fit the diagnostic criteria for TGA and seizures were ruled out by a normal sleep-deprived electroencephalogram (EEG). Magnetic Resonance Imaging (MRI) of Brain showed the presence of a right frontal meningioma. We conclude that she suffered from TGA secondary to right frontal meningioma, a rare association of which only a handful of cases have been reported worldwide.

Keywords: Brain neoplasms, Meningioma, Transient global amnesia.

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INTRODUCTION:

Transient global amnesia (TGA) was first described by two authors in the 1950s.[1, 2] It is a syndrome of retrograde amnesia which should completely resolve within 24 hours. Also, during this episode, the patient should have no other cognitive or neurological deficits. Once this episode has subsided, the patient usually has no recollection of the events. The most common causes of TGA are migraine variant, transient ischemic attack, emotional stress, severe pain, physical exertion or vasospasm.[3,4] Transient global amnesia occurring as a presenting feature of a brain tumour is extremely rare, with fewer than 20 cases reported worldwide till 2015.[5] The case of a 65 years old female, who presented with TGA to our hospital is presented here.

CASE REPORT:

A 65 years female, right handed, with no known co-morbid conditions, presented to our Emergency Room with complains of two episodes of transient amnesia. Each episode had lasted for 4-5 hours. The first episode occurred two days prior to admission and the second episode occurred on the day of admission.

Prior to the onset of both episodes, she was carrying out her routine activities at home. There was no history of any physical or emotional stress before these episodes. Her family members noted that she suddenly became very confused. She was unable to remember the day and the date. She also had no recollection of what task she was performing and what her plans for the day had been. Throughout the episode, she repeatedly kept asking her husband what was happening. The family noted no other neurological symptoms during these episodes. Both attacks resolved in 4-5 hours after which the patient had no recollection of the attack. There was no associated headache or loss of consciousness.

She had no significant past history and was on no medications. She had no history of head injury, unconsciousness or seizures previously. She was a housewife with no family history of any neurological disorder.

On examination, she was vitally stable. Her Glasgow Coma Scale (GCS) was 15/15 with intact cranial nerve, motor, sensory and cerebellar examinations. On Frontal Lobe Assessment, her conceptualization, lexical fluency, orientation to time and place, speech and emotional state were normal with absent released reflexes. Calculation was impaired leading to a Mini Mental State Examination (MMSE) score was 27/30.

A diagnosis of TGA was considered according to diagnostic criteria. (Table 1)[6] Keeping in mind the association with vasospasm and differential diagnosis of Transient Ischemic

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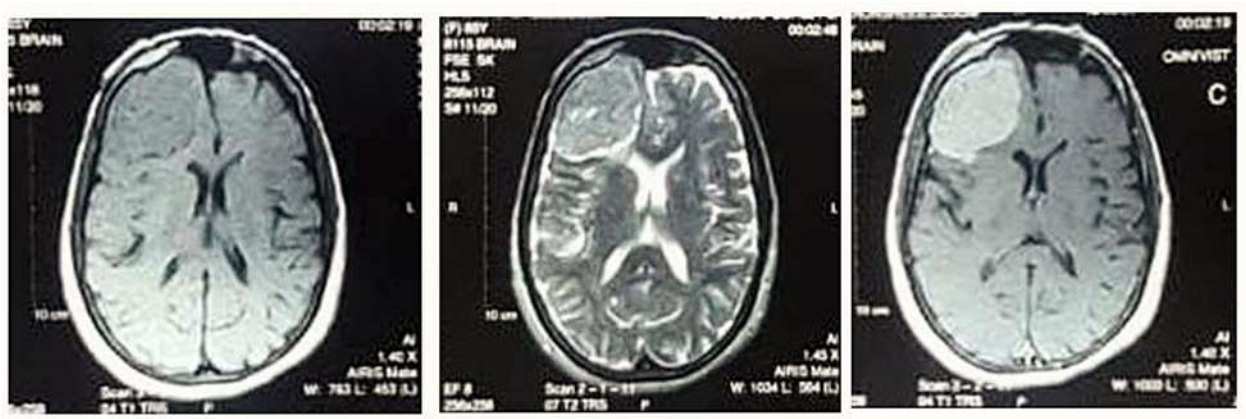
Figure 1: Computed Tomography (CT) Scan Brain Plain (Axial view) showing a mixed density lesion in the right frontal lobe

Table 1: Hodges and Warlow Criteria for diagnosis of transient global amnesia [6]

Hodges and Warlow Criteria for Transient Global Amnesia
Attacks must be witnessed
There must be anterograde amnesia during the attack
Cognitive impairment is limited to amnesia
No clouding of consciousness or loss of personal identity
No focal neurological signs/ symptoms
No epileptic features
Attacks must resolve within 24 hours
No recent head injury or active epilepsy

Figure 2: Magnetic Resonance Imaging (MRI) Brain (Axial View) showing a right frontal meningioma



Attack (TIA), neuro-imaging was carried out. Computed Tomography (CT) Scan Brain Plain showed a well circumscribed, mixed density lesion in the right frontal lobe suggestive of a meningioma (Fig 1). Magnetic Resonance Imaging (MRI) of the Brain with contrast showed an extra-axial area of abnormal signal intensity in the right frontal lobe that was isointense on T1 weighted image, mixed intensity on T2 weighted image with homogenous contrast enhancement (Fig 2). These findings represented a right frontal lobe meningioma.

All other investigations including a complete blood count, renal and liver function tests, metabolic panel, hepatitis B surface antigen, antibodies to hepatitis C virus, random and fasting blood sugars, glycated haemoglobin, fasting lipid profile, electrocardiography and echocardiogram were normal. An electroencephalogram that the patient had brought with her was normal. Considering the differential diagnosis of Transient Epileptic Amnesia (TEA), a sleep-deprived electroencephalogram was also performed which was normal for age and state.

A neurosurgery consultation was taken and surgery planned. Other than the above described episodes of amnesia, the patient experienced no further episodes. Following her surgery, she will be reassessed in the Neurology clinic.

DISCUSSION:

Meningiomas are amongst the most common of all central nervous system (CNS) tumours, accounting for approximately one third of all primary brain and spinal cord tumours.[7] A study conducted in Gwalior, India found that meningiomas comprised 26.17% of all brain tumours investigated during the study period.[8] These tumours arise from the arachnoid cap cells in the meninges and are easily diagnosed through neuro-imaging. Meningiomas commonly occur in the elderly (Age greater than 65 years) and in females.[9]

Meningiomas produce their typical symptoms through various mechanisms. They can cause symptoms by compressing the underlying brain parenchyma or cranial nerves.[10] Another mechanism of injury is direct invasion of the underlying structures, during which they may cause

vascular injuries as well.[11] The mechanism of injury as well as the site of the meningioma will determine the signs and symptoms that patients present with. The most common symptoms associated with meningiomas are headache due to increased intracranial pressure, focal neurological (including cranial nerve) deficits or generalized and partial seizures caused by focal mass effect. In frontal lobe or parasaggital meningiomas, personality changes, confusion and altered level of consciousness are often seen. These patients are often misdiagnosed as dementia or depression.[12] Our patient was diagnosed with a frontal lobe meningioma; however, she failed to show any of the signs or symptoms mentioned above.

Transient global amnesia is rarely associated with brain tumours. The pathophysiology still remains unclear with the consensus being that hippocampal dysfunction causes this particular phenomenon.[13] However, cases have been reported of TGA occurring with lesions distant to the hippocampus.[14]

Since meningiomas can cause seizures, both focal and generalized, and the closest differential to TGA is Transient Epileptic Amnesia (TEA), it is essential that seizures be ruled out in all patients presenting with episodic amnesia. In our patient, this is achieved by applying the diagnostic criteria for TGA (Table 1) and also performing a sleep deprived EEG. The EEG was normal for the patient's state and age. The duration of the patient's symptoms (4-5 hours) were greatly exceed the duration of an attack of transient epileptic amnesia (Usually less than 1 hour).[15]

On the basis of thorough investigations and MRI findings, it was concluded that this patient had transient global amnesia secondary to a frontal lobe meningioma. It is a rare association, but potentially treatable, and should be kept in mind when investigating patients with a similar presentation.

CONCLUSION:

Transient global amnesia may rarely occur as a consequence of space occupying lesions in the brain, even in lesions remote from the hippocampus. Imaging of the brain should be performed in all patients presenting with episodic amnesia and appropriate investigations should also be carried out to exclude seizures.

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Commentary

E-Learning Among University Students During COVID-19

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Somewhere in the beginning of March 2020, State Government suddenly announced the closure of all educational institutions as a preventive measure to restrict the spread of novel coronavirus. It has been over five months since the government has completely shut down the educational institutions. Recently there is an announcement that Universities will reopen in the mid of September 2020. As the days pass by with no instant solution to stop the outbreak of covid-19, the educational processes came to a standstill due to closure of the universities and colleges. In order to restore the ongoing process of learning majority universities in Pakistan have now quickly shifted to e-learning. This pandemic has transformed the old methods of teaching with the new technology driven methods.

E-learning according to a research is electronically enabled learning.[1] It includes the use of information and communication technologies to get access to online teaching or learning resources. Simply the digital technology driven learning is called e-learning. Few researchers have further narrowed down the definition by referring any learning that is enabled by web or internet.[2, 3]

Researches have described two modes of e-learning 'synchronous' or 'asynchronous' depending upon the timing of interaction. The synchronous timing allows interaction between instructor and learners or between learners.[4] The asynchronous timing also allows interaction with the instructor or between learners at different times.[5]

The adoption of e-learning among university students has several advantages and limitations. Benefits of e-learning are:

1. It is flexible. Students have the choice of choosing the time and place that suits them.[6]

2. Students are not required to travel to their institutions it is therefore cost effective. It can cater maximum number of students without the need of new buildings and classrooms.

3. Synchronous type of e-learning method allows for discussion among instructors and students at the same time through different tools such as videoconference or chat rooms. Thus offers instantaneous feedback.[5]

4. Asynchronous type of e-learning allows students to study at their own pace, slow or quick. It therefore decreases stress among students who are slow learners.[7, 8]

5. E-learning offers ease of access to a plethora of information that is available online.

There are some limitations of e-learning as well.

1. E-learning doesn't offer much when it comes to improving communication skills. Student might lack the essential skills to deliver the knowledge to others despite having excellent academic record.

2. Asynchronous type of e-learning allows interaction through thread discussion or via emails, therefore it lacks interaction at the same moment and the instructors are not able to receive instant feedback from students and vice versa.[5]

3. It is difficult to control cheating.

4. E-learning is not an appropriate technique of education especially in those scientific fields which include practical work as well. Therefore researchers are of the opinion that e-learning is beneficial for social science and humanities and offers limited benefits in fields where practical skills are of utmost importance like medical science, pharmacy, and physiotherapy.

5. Heavy use of some websites make them congested, as well as some websites require monthly subscriptions which may lead to unanticipated loss of time and money.[9,10]

COVID-19, was revealed in December 2019.[11] Face to face transmission was discovered by clinical analysis. [12-14.] This outbreak has imposed an online platform in all aspects of human life such as business, marketing, educational institutes.[15]

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In educational institutes; the E-learning involves digital tools for learning as well as teaching which comes with the ease of studying anywhere and anytime. Despite some challenges e-learning has a strong impact in teaching and learning. Its full implementation in universities will allow students, faculty members and administrators to enjoy its benefits.

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Precautions and Safety Measures at Workplace During Pandemic

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Pandemic is a worldwide disease outbreak, caused by various types of agents for example influenza and coronaviruses. Recent pandemic has been the third outbreak of coronavirus COVID-19 (Corona virus disease-19) declared by World Health Organization (WHO), spread in more than 213 continent including Pakistan.[1] Transmission of disease during pandemic expected in workplaces not only from patient to healthcare personnel but also between the co-workers and people of general public and individuals from other workplaces.[2] In Pakistan, total number of positive cases: 302,424 of COVID-19 were reported and 6,389 deaths were confirmed till 15th September 2020.[3] Unfortunately presently there is no vaccine available against COVID-19 to prevent this disease. The transmission and spreading of this virus in different countries is suppressed by testing and take care of patients, limiting travel, stopping huge gatherings such as concert, schools, sports events and quarantine the infected person. [4] This pandemic placed a huge burden on all section of society including companies and employee workers by suspending their working activities and implementing new measures and practices in very small period of time during this crisis. The European Union member's countries established numbers of procedures and measures for the prevention and spreading of pandemic in working places.[5] Major precautions and safety measures should be integrated in the workplace which covers all risks assessment by European Union and National Occupational Health and Safety Regulation and are as follows. [6]

- Instruct employees, frequently wash their hands with soap and water for at least 20 seconds or used alcohol based hand sanitizer which contains 60-90% alcohol.
- Encouraging hand hygiene by placing hand sanitizer in multiple locations and in common areas of working place.
- Provide surgical masks to employees.
- Sneezing etiquettes: Ensure that they cover their mouth and nose with tissue or sleeves while coughing or sneezing.
- Check, follow and share the instructions from the concern authorities in the group; where the meetings or events are arranged.
- Brief the employees, workers and co-workers that anyone with low grade fever (37.3?C or more) and mild cough should stay home or work from home.
- Before starting work, disinfect your desktop/ laptop and table.
- Stop sharing food with your colleague and co-workers and eat distantly from others.
- Develop and approve the plan and strategies to prevent contamination of disease during meeting.
- Replace face to face meetings in teleconferences or online.
- Confrontation meetings could be scaled down and less people attend the meeting.
- Avoid direct touching the lift buttons, use tissue for handling and ensure that there are not more than two people in the lift.
- Maintain social distancing at the time of interaction with other people and avoid shaking hands.

All of the above mentioned guidelines can halt the transmission of virus and help the employers and employees to work safely at work place during COVID-19 outbreak.

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