pISSN: 2220-7562
eISSN: 2617-9482
CODEN: JBUMB7
Recognized by HEC

JBUMDC

Journal of Bahria University Medical & Dental College

Volume 12 Issue 3, July - September 2022

Bahria University Health Sciences Campus Karachi
Adjacent PNS SHIFA, DHA Phase II, Karachi

JBUMDC
Journal of Bahria University Medical & Dental College
Peer Reviewed Multidisciplinary Quarterly Published Journal
ISSN (print): 2220-7562, ISSN (online): 2617-9482, CODEN: JBUMB7
Recognized by HEC
Online edition is available at URL: https://jbumdc.bahria.edu.pk,
Indexed with Index Medicus for the Eastern Mediterranean Region (IMEMR),
https://vlibrary.emro.who.int/journals/jbumdc-journal-of-bahria-university-medical-and-detal-college/
ROAD Directory of Open Access Scholarly Resources at https://portal.issn.org/resource/ISSN/2617-9482
Pakmedinet at www.pakmedinet.com/jbumdc,
Google Scholar at https://scholar.google.com.pk/,
Crossref at https://doi.org/10.51985/aluu2996
ICMJE at https://www.icmje.org/journals-following-the-icmje-recommendations/#J
Bahira University DSpace Repository at http://111.68.99.22:8080/xmlui/handle/123456789/6388,
Pakistan Scientific and Technological Information Center (PASTIC) at http://pastic.gov.pk/

Correspondence Address:
Editor, JBUMDC, Bahria University Medical & Dental College, Adjacent PNS SHIFA,
DHA Phase II, Karachi Pakistan
+92-21-35319491-9
https//jbumdc.bahria.edu.pk
editor.bumdc@bahria.edu.pk
https://www.facebook.com/jbumdc/, https://www.facebook.com/journal.bumdc.7
Published by: Bahria University Medical & Dental College

JBUMDC

Journal of Bahria University Medical & Dental College

Recognized by HEC

JBUMDC Journal of Bahria University Medical & Dental College
Volume-12, Issue-3. July - September 2022

CONTENTS

Editorial **Open Access**

Violence and Litigations Against Health Care Workers in Pakistan

Iqbal Hussain Udaipurwala

How to cite this Article:
Udaipurwala IH, Violence and Litigations Against Health Care Workers in Pakistan. J Bahria Uni Med Dental Coll. 2022;12(3):116-117 DOI: https://doi.org/10.51985/JBUMDC202281

Over the past two decades, litigations as well as violence against the health care workers has followed an exponentially incremental trend around the globe.[1] Although doctor and also other medical staff is often considered as "angel" who belongs to a noble profession but still violence against them throughout the world is a matter of concern.[2] This violence against them can be physical like assault but mostly in the psychological form like verbal threat, harassment, bullying, litigation etc.[3] The current situation of Pakistan is not much different from the rest of the world.[4]

The history of medical litigation dates back to very ancient times but in modern civilized society in 1765, Sir William Blackstone published "Commentaries on the Laws of England" which described cases of "Mala Praxis," that is neglect or unskillful management of a physician or surgeon.[5] In United States of America, first recorded medical malpractice lawsuit took place in 1794 where a patient died of a surgical complication.[5] During the 19th century, number of litigations against medical malpractice started increasing as it was an attractive area for aggressive lawyers. Majority of the lawsuits were against error of treatment related to amputation, dislocations and fractures. During the 20th century, majority of the lawsuits were related with "*error of commission*" that is when a physician had done something wrong. As a result of this physicians started doing "*defensive medicine*" i.e. to be sure about diagnosis and treatment, doing extra laboratory tests and radiological investigations and doing less intervention. This led to a new era of lawsuits against "*error of omission*" that is when a physician had failed to do something right.

In Pakistan, violence against healthcare worker has increased tremendously during recent past in both public sector as well as private sector hospitals.[6,7] In public sector hospitals main cause for violence is because of inadequate facilities like lack of drugs, long waiting time for surgeries, lack of cleanliness and shortage of medical staff and doctors etc. Because healthcare workers are in forefront, patients and their attendants think that they are responsible for all these deficiencies. In fact, all of these deficiencies are of administrative nature and healthcare workers are helpless to solve these problems. In private hospitals main cause for violence is financial and monetary aspect of treatment and they want to get discounts or even total deduction of whole billing amount. When a patient is brought in private hospital in critical condition, attendants say, do whatever is required without considering its cost and at the end if the patient dies, they start violence just to get benefit in billing amount. Overload and lack of time is another important factors in public as well as in private sector hospital due to which proper counselling of the patients and their attendants is not done properly. Patients and their attendants are often unacquainted with the disease and its consequences which finally ended in violence, if the results are not according to their desire. According to one study conducted at 4 major public sector hospitals of Karachi, 74.9% of the doctors have encountered workplace violence.[8] Another study conducted at a public sector hospital in Lahore showed 73.8% of doctors and nurses were victims of violence in the preceding 12 months of the study.[9] To reduce violence, Government of Pakistan in 2019 has amended the laws related with any sort of violence against healthcare worker or hospital property in public or private sector hospital. Now, it is a non-bail able offense with punishment of 6 months to 10 years. Many of the healthcare workers and hospital staff are still unaware of these laws, so this information should be disseminated appropriately. Secondly law enforcement agencies should implement these laws strictly and take appropriate action against those who are involved in such acts.

Complication during or after surgery may occur and it is not always because of the surgeon's negligence. Many factors are involved in it like environmental, patient's general condition, advance condition of the disease and even patient's own carelessness in not following doctor's advice. Whenever a surgical complication occurs, most of the patients and their attendants think it is only because of surgeon's negligence and they start violence and even go to court of law for litigation. Such violence and litigations can be prevented or reduced by taking proper "Informed consent" which should contain proper information about the disease, its treatment options and its consequences. Obtaining informed consent is very critical and necessary in medical practice and should contain all three domains; information, comprehension and voluntariness. Majority of the hospitals in Pakistan have a

Iqbal Hussain Udaipurwala
Professor and Head of the ENT Department
Bahria University Medical & Dental College, Karachi
Email: iqbal.bumdc@bahria.edu.pk

Received: 30-May-2022
Accepted: 09-June-2022

general "consent form" for surgical procedure that is used in all types of surgeries. Separate consent form for each surgery should be designed mentioning all details related with the disease process, its treatment options, consequences and complications of the surgery and it's use will reduce litigation cases and of course violence as well.

Use of electronic media for storing health records and its sharing with other colleagues has brought convenience in our life at one end but on the other end has posed serious privacy threats.[10] The security of the medical data is facing growing challenges due to fast upsurge of data volume and development of storage cloud platforms. The revelation of patient's private information on electronic media has also posed serious consequence leading to increase in litigation cases against healthcare workers. Therefore protection of the patient's private information is very important consideration in the field of medical data sharing and distribution.

The cost involved in litigation cases in lawsuits effects not only individual professional but also on overall healthcare facilities budget.[11] Due to defensive medicine and use of extra tests as a result of medico-legal cases, overall healthcare cost has been increased much. But still defensive medicine is the only way to avoid malpractice lawsuit. Defensive medicine is similar to "defensive driving," when a driver expects likely dangers then he automatically takes appropriate action to reduce the risk of an unfortunate accident. Defensive medicine is defined as actions that healthcare providers take in order to protect themselves from malpractice lawsuits rather than actions benefitting the patient.[12] It has been observed in healthcare system around the globe and found to have increased during the last two decades.

Following are the suggestions to reduce violence and litigations against health care workers in Pakistan:

- Strict compliance of laws against those responsible and involved in violence of any sort in hospitals and clinics.
- Lawsuits against healthcare workers should not be prosecuted in normal courts rather separate courts should be established for this purpose with judges having special experience for such medical cases.
- Government controlling authorities for healthcare like Pakistan Medical Commission (PMC), or Health Department should come forward and take responsibility to deal with cases of medical malpractice on their own rather to go in court of law.
- Security guards in public sector hospitals and clinics should be adequate to deal with people involved in violence on the spot.
- All healthcare worker including doctors, nurses and paramedical staff should have an insurance to bear cost of court proceedings and penalty charges imposed on them and must be provided by the employers.
- Communication skill workshops should be repeated regularly to train healthcare worker regarding counselling, breaking bad news, taking informed consent and dealing with aggressive crowd

Authors Contribution:
Iqbal Hussain Udaipurwala: Substantial contributions to the conception criticaly evaluation of intellectual content, final approval of the version to be published

REFERENCES

1. La Russa, R.; Viola, R.V., D'Errico, S.; Aromatario, M.; Maiese, A.; Anibaldi, P.; Napoli, C.; Frati, P.; Fineschi, V. Analysis of Inadequacies in Hospital Care through Medical Liability Litigation. Int. J. Environ. Res. Public Health, 2021; 18: 3425. https://doi.org/10.3390/ ijerph18073425
2. Ghosh K. Violence against doctors: A pandemic in the making. European Journal of Internal Medicine. 2018; 50: e9–e10. https://doi.org/10.1016/j.ejim.2017.08.017
3. Ranjan R, Meenakshi, Singh M, Pal R, Das J, Gupta S. Epidemiology of violence against medical practitioners in a developing country (2006–2017). Journal of Health Research and Reviews. 2018; 5(3): 153-60. https://doi.org/ 10.4103/ jhrr.jhrr_84_17
4. IA, M. Medicolegal issues in neurology Practice in Pakistan , 2020; 15(3): 1-3.
5. Berlin L. Medical errors, malpractice, and defensive medicine: an ill-fated triad. Diagnosis (Berl). 2017; 4(3): 133-139. https://doi.org/: 10.1515/dx-2017-0007.
6. Mateen S. Work Place Violence Reported by Student Nurses through Health Professionals in Clinical Setting. Ann. Pak. Inst. Med. Sci. 2014; 10(4): 215-217.
7. NICVD doctor shot at, wounded by policeman. https://www.dawn.com/news/1564450/nicvd-doctor-shot-at-wounded-by-policeman.
8. Nayyer-ul-Islam, Yousuful-Islam M, Farooq MS, Mazharuddin SM, Hussain SA, Umair-ul-Islam. Workplace violence experienced by doctors working in government hospitals of Karachi. J Coll Physicians Surg Pak. 2014; 24(9): 698-9.
9. Imran N, Pervez MH, Farooq R, Asghar AR. Aggression and violence towards medical doctors and nurses in a public health care facility in Lahore, Pakistan: A preliminary investigation. Khyber Med Univ J., 2013; 5(4): 179-184.
10. Su J, Cao Y, Chen Y, Liu Y, Song J. Privacy protection of medical data in social network. BMC Med Inform Decis Mak. 2021; 21(Suppl 1): 286. https://doi.org/10.1186/s12911-021-01645-0
11. Treglia M, Pallocci M, Passalacqua P, Giammatteo J, DeLuca L, Mauriello,S, Cisterna AM, Marsella LT. Medical Liability: Review of a Whole Year of Judgments of the Civil Court of Rome. Int. J. Environ. Res. Public Health 2021, 18, 6019. https://doi.org/10.3390/ ijerph18116019
12. Lykkegaard J, Andersen MKK, Nexoe J, Hvidt EA. Defensive medicine in primary health care. Scand J Prim Health Care. 2018; 36(3): 225-226. https://doi.org/ 10.1080/ 02813432. 2018. 1499483

Original Article **Open Access**

Efficacy of Atropine to Blunt Unopposed Vagal Activity in Prevention of Hypotension in Parturients Undergoing Spinal Caesarean Section

Muhammad Salman Maqbool, Shumaila Ashfaq

ABSTRACT:

Objective: To determine efficacy of prophylactic atropine to blunt un-opposed vagal activity in prevention of hypotension associated with caesarean spinal block in first 15 minutes.

Study Design & Setting: Randomized controlled interventional study (purposive sampling method) done at Islam Teaching Hospital, Sialkot from 03-3-2021 to 11-8-2021

Methodology: Chairman Ethics Review Board, Islam Medical College, Sialkot vide letter No.2021-04/A, dated 03-3-2021, consented for study. G-power statistics v3.1.9.2, employing chi-square goodness of fit test value of 11.07, total sample was 144 bunched into two prophylactic treatment groups by using computer generated numbers (group-A, Inj. atropine 0.5mg and group-B, Inj. Placebo (control) planned for elective caesarean spinal delivery. Primary study variable being hemodynamic stability (pulse, blood pressure) in first 15 minutes after placing block. Independent-Samples Kruskal-Wallis Test used to compare systolic blood pressures between groups for association. Chi- square hypothesis test, was done with P-value <0.05 considered as statistically significant. SPSS analysis was done with v.21

Results: In Atropine group-A, there was rather a 11% increase in mean heart rate at 15 minutes mark (statistically significant) than the mean baseline value while in group-B (placebo)similar values parameter showed a 4.7% decline in mean heart rate value. In group-A, mean systolic blood pressure value declined only by 12.2% at 15 minutes mark from baseline value whereas in group-B, a decline of 13.2% was noted.

Conclusion: Prophylactic bolus of atropine against un-opposed vagal activity provided stable hemodynamic values in cesarean spinal delivery.

Key words: Atropine, Co-load, hypotension, Obstetric anaesthesia, Subarachnoid Anaesthesia.

How to cite this Article:
Maqbool MS, Ashfaq S. Efficacy of Atropine to Blunt Unopposed Vagal Activity in Prevention of Hypotension in Parturients Undergoing Spinal Caesarean Section. J Bahria Uni Med Dental Coll. 2022; 11(3):118-123 DOI: https://doi.org/10.51985/JBUMDC202201

INTRODUCTION

The spinal block is the widely practiced anaesthesia technique due to its wide safety margin.[1] It is also currently the method of choice for elective caesarean section, because it avoids risks linked with general anesthesia, such as full stomach (risk of acid aspiration syndrome), mask ventilation / intubation difficulties and general anesthesia drugs causing fetal depression, secondly it has the advantages of reducing maternal mortality, low dose of local anesthetic agent, maternal-fetal bonding, complete dense block, including decreased blood loss, and excellent postoperative pain control compared to general anesthesia etc.[2,3] It is an invasive procedure that could be associated with hypotension (33%) and bradycardia (33%) with an incidence of up to 75% of spinal hypotension in parturient who receive spinal anesthesia.[4,5] The cardio-vascular physiological response following spinal anesthesia results either from extent of sympathectomy or un-opposed parasympathetic tone. The systemic vasodilation induced by sympathetic blockade after sub-arachnoid block, results in venous pooling of blood and reduction in the systemic vascular resistance, has been regarded as the predominant mechanism for hypotension. The sympathetic block extent is related to the cranial spread of the local anesthetic within the subarachnoid space, narrowing of the sub-arachnoid spaces due to compression effect of uterus along with the aorto-caval compression and due to higher sensitivity to local anesthetics are main reasons for higher incidence of hypotension in parturient, in comparison to non-obstetric patients. In different studies, it was postulated that in the setting of spinal anesthesia, reduced venous return along-with unopposed vagal tone

Muhammad Salman Maqbool,
Professor & Head of Department of Anaesthesia & Intensive Care,
Islam Medical & Dental College, Islam Teaching Hospital, Sialkot
Email: muhammadsalman590@gmail.com

Shumaila Ashfaq
Assistant Professor, Department of Anaesthesia,
Islam Medical & Dental College, Sialkot
E-mail: shumailaashfaq24@gmail.com

Received: 03-Jan-2022
Accepted: 29-Jun-2022

results in variable degree of hypotension and bradycardia,[6] with blockade of cardioaccelerator fibers (sympathetic nerve fibers from T1 to T4,), and possibly due to reversal of the Bainbridge reflex (may result in cardiac arrest).[7]

Currently various techniques have been adopted to overcome the degree of hypotension and bradycardia administration of vasoactive medication, pre or co-loading of intravenous fluids, other methods such as right pelvic wedge placement, and calf compression devices.[7,8]

Anticholinergic (atropine) is an ester of aromatic acid in combination with organic base. The ester linkage is essential for effective binding of the anticholinergics to the acetylcholine receptors. This competitively blocks binding by acetylcholine and thus prevents receptor activation. Atropine being a tertiary amine, the naturally occurring (laevorotatory form) is active, but the commercial mixture is racemic. Its intravenous administration, demonstrates a pattern of increase in heart rate and systolic blood pressure and lower diastolic pressure resulting in slightly increase cardiac output and decrease central venous pressure.[9] The prophylactic atropine averts blunted Bain-bridge reflex effect, the net effect being increased heart rate and improved cardiac output after sympathetic spinal block.[7] In another study employing parturient positioning with table tilt (along with wedge under right hip) to prevent the effect of aorto-caval compression, atropine was given prophylactic atropine in caesarean section as a combination technique to prevent sympathetic block hypotension.[8]

The efficiency of prophylactic atropine in the elderly population has been researched, but inadequate information is there regarding its use in parturients planned for caesarean section under intra-thecal block.[10] Therefore a study was designed to evaluate the efficacy of atropine in prevention of hypotension in parturient undergoing spinal caesarean section in first 15 minutes after spinal injection.

METHODOLOGY:

This randomized controlled interventional study (purposive sampling method) was conducted whereby, term parturient due for elective caesarean spinal delivery were enrolled at Department of Anaesthesia & Intensive Care, Islam Medical & Dental College, Islam Teaching Hospital, Pasroor Road, Sialkot from 03-3-2021 to 11-8-2021. The Chairman Ethics Review Board, Islam Medical & Dental College, Sialkot vide letter No.2021-04/A, dated 03-3-2021, consented for this study. Sample size was considered by G-power statistics v3.1.9.2, taking effective size w-value of 0.3, á-error of 0.05 and 80% power to detect a true effect with Df value 5 and employing chi-square goodness of fit test value of 11.07, the total sample came out to be 144 cases. Pre-anesthesia evaluation and informed written consent was taken in all cases. Using the sequence of elective surgery schedules subjects were randomly bunched into two prophylactic treatment groups by using computer generated numbers into (group-A, Inj. atropine 0.5mg and group-B, Inj. Placebo (control) both constituted to make a 3ml solution, with 72 cases (computer generated) for this randomized controlled interventional study. Parturient were not aware to which group they were allocated. Inclusion criteria was ASA I or II, term parturient age between 18-40-year for elective Pfannenstiel incision surgery under sub-arachnoid block, baseline heart rate between 80-90/minute. Exclusion criteria was coagulation disorder, preeclampsia, arrhythmias such as atrial fibrillation, tachycardia (heart rate baseline value above 100-110/ minute), HELLP syndrome, sepsis at the site of injection, indeterminate neurologic disease, raised intracranial pressure, allergy to anesthetics, discopathy, and fixed cardiac output state e.g., aortic stenosis. All Patients fasted and were pre-medicated with (ranitidine 150 mg at night before the operation) according to ASA guidelines. Per-operatively,18G intravenous lines were placed, baseline vitals (blood pressure, heart rate, and oxygen saturation) noted and all patients received crystalloid isotonic fluid as co-load. Spinal anesthesia with bupivacaine spinal 0.75% hyperbaric (12mg) in sub-arachnoid space over a period of 15 seconds was managed by consultant anesthesiologist employing standard aseptic technique with 25g quincke needle at L3-4 level in left lateral position and placed supine after block. The anesthetist was blinded to prophylactic medication (given by nurse anesthetist at time of giving sub-arachnoid block injection) provided by fellow consultant anesthetist in sealed labelled syringes and both were part of study team with fixed roles. The block was evaluated by pin prick in midline(sensory), modified bromage scale(motor) at 3 minutes, while the autonomic block was checked by spirit dipped swabs to check for cold and warm sensation. Pulse, systolic and diastolic blood pressure was monitored at 1,3,5,7,9,11,13 and 15 minutes interval following administration of prophylactic medication for hemodynamic stability (the primary outcome variables of the study). The primary study variable being hemodynamic stability (pulse, blood pressure) in first 15 minutes after placing block. The notable secondary outcome variables being need of vasopressors, anticholinergic drugs and adverse effects. Hypotension was defined in study as a decrease in mean blood pressure of less than 12% from the baseline value or systolic blood pressure < 90mmHg) and treated with intra-venous bolus of vasopressors. Inj. atropine was given for heart rate < 60 beats/minute or 35% decrease from baseline value. Hemodynamic parameters were compared with baseline values among the groups. Independent-Samples Kruskal-Wallis Test was applied to compare systolic blood pressures between group-A(atropine) and group-B(placebo) for association. Chi- square hypothesis test, was done to determine if there is a statistically significant difference between expected and observed frequencies with P-value <0.05 considered as statistically significant. SPSS analysis was done with v.21. Null hypothesis i.e., a claim we want

to test is, H_0: Atropine prophylactic use for hemodynamic stability in cesarean section under spinal anesthesia do have any clinically significant effect, while alternate hypothesis, H_a: Atropine prophylactic use for hemodynamic stability in cesarean section under spinal anesthesia do not have a clinically significant effect, were the hypothesis of the study.

RESULTS:

The mean age(years) in group-A(atropine) & B(placebo) in study being 26.59(SD of 4.22) and 26.72(SD of 3.22) respectively. Pulse variation and systolic blood pressure readings in both groups are depicted in table-1 and 2 respectively. The mean baseline and at 15 minutes diastolic blood pressure(mmHg) in group-A, being 85.01(SD of 12.48) and 64.97(SD of 14.39) whereas similar readings in group-B, being 88.61(SD of 15.38) and 67.56(SD of 14.37) respectively and showed no marked statistical difference. The heart rate variations of both groups are shown in graphical way in graph-1.

The distribution and analysis done by Independent-Samples Kruskal-Wallis Test of systolic blood pressure (mmHg) is the same across all categories in (Atropine group-A and Placebo group-B) sig. value was .478(significance level was .050) and we retain the null hypothesis. Pearson correlation coefficient value of 0.439 & 0.446 in group A & B, of study was also significant statistically at 0.05 & 0.01 level (2–tailed) as regard to heart rate variation from baseline value respectively. On application of Pearson Chi-square test 0.015 value was calculated in group-A data, the output resulted concludes interpretation of the P-value of 0.975 at df-2(degree of freedom) which indicates that there is insufficient evidence to reject the null hypothesis. In placebo group-B, high chi-square computed was .501 due to which expected and observed were not close and the model was a poor fit to the systolic blood pressure readings in comparison to baseline value data and cannot reject null hypothesis. The systolic blood pressure variations of both groups A and B are depicted in graph-2.

DISCUSSION:

Bradycardia is a presentation of cardio-vascular collapse after neuraxial block anaesthesia. A wide number of etiological factors are postulated such as the sudden shift of cardiac autonomic balance, myocardial pacemaker cells reflex arc activation, Bainbridge reflex, hypoxia and respiratory apnoea, triggering of cardioinhibitory receptor and the pacemaker-stretch reflex i.e., decreased stretch is evident as bradycardia, paradoxical response of stretch receptors in sinus node (bezold jarisch reflex) and baroreceptor mediated activation of vagal reflex arc. No supportive data exists as to whether cardio-inhibitory receptors or bezold jarisch reflex is solely responsible for the event.[11] Cardiac accelerator fibres T_1-T_4 blockade modifies autonomic nervous system cardiac input leading to un-opposed parasympathetic activity (at Sino-atrial and atrioventricular node) may manifest as bradycardia and asystole and the "reverse" Bainbridge reflex explains decreases in heart rate noticed under condition of decreased venous return e.g., in intra-thecal block.[12,13] In another study it was backed to practice a rationale for cardio-vascular changes (bradycardia and hypotension) following intra-thecal block by treating bradycardia immediately with anti-cholinergic agent, if hypotension persists it is managed by appropriate vasopressors.[13] Similar practice was implemented in our study by using prophylactic atropine intra-venously at time of spinal block.

Hypotension associated with neuraxial block is secondary due to sympathetic block. The systemic vascular resistance decreases, peripheral vasodilation with redistribution of the central blood volume to splanchnic circulation and lower limbs along with decrease in myocardial contractility. The cause of bradycardia is however less clear, but there is a shift towards vagal predominance with sub-arachnoid anaesthesia. There is evidence that cardiac afferent fibre activation helps to preserve diastolic filling time during relative decrease in venous return and that bradycardia is associated with echocardiographic evidence of small left ventricular chamber size.[14]

In the group-A of study, there was rather 11% increase in mean heart rate at 15 minutes mark (statistically significant) than the mean baseline value (91.25 vs 100.85) as in only 17(23.6%) of cases repeat bolus dose of atropine was given while in 55(76.4%) cases no atropine was needed. In Placebo group-B, in 30(41.7%) cases repeat atropine bolus intra-venously was used, while no atropine was used in 42(58.3%) of cases, while there was 4.7% decline in mean heart rate value at 15 minutes in comparison to baseline value (105.58 vs 101.93) respectively. In the Atropine group-A, mean systolic blood pressure value declined only by 12.2% at 15 minutes (chi-square value of .015) from baseline value (131.51 vs 115.45) whereas in Placebo group-B there was a decline of 13.2% in mean systolic blood pressure (chi-square value of .501) at value 15 minutes from baseline value (135.51 vs 118.666) respectively. Therefore group-A, showed better hemodynamic (heart rate and systolic blood pressure) stability and so we cannot reject null hypothesis in our study. In group-A & B the mean decrease in diastolic blood pressure at 15 minutes from baseline value was 24.7% and 23.9% respectively which was statistically insignificant.

In group-A & B vasopressor was given in 36(50%) of cases and not used in 36(50%) cases whereas, similar values in group-B, being 38(52.78%) and in 34(47.2%) of cases respectively. In 4(5.6%) cases in group-B, severe hypotension occurred requiring colloids and measures to increase venous return. In group-A, colloid fluid was administered in 1 case only (0.69%). A single case was of late post-partum hemorrhage (placenta previa) where intra-venous fluids were rushed along with bolus doses of vasopressor agents.

Table-1: Pulse variations in both groups A and B. (n=72)

	Minimum	Maximum	Mean	Std Deviation
Baseline pulse / minute (Atropine / Placebo) group A & B	63 / 78	111 / 147	91.25 / 105.58	10.476 / 15.422
Pulse at 01-minute (Atropine / Placebo) group A & B	68 / 65	130 / 141	98.06 / 102.99	11.640 / 15.756
Pulse at 03-minute (Atropine / Placebo) group A & B	80 / 72	147 / 161	105.00 / 102.83	13.905 / 17.082
Pulse at 05-minute (Atropine / Placebo) group A & B	77 / 60	151 / 163	106.21 / 103.10	14.918 / 17.189
Pulse at 07-minute (Atropine / Placebo) group A & B	81 / 68	139 / 140	104.67 / 102.49	12.635 / 15.054
Pulse at 09-minute (Atropine / Placebo) group A & B	71 / 77	145 / 138	104.46 / 102.67	14.213 / 13.346
Pulse at 11-minute (Atropine / Placebo) group A & B	71 / 78	139 / 134	103.67 / 101.99	12.450 / 12.540
Pulse at 13-minute (Atropine / Placebo) group A & B	61 / 78	132 / 132	101.76 / 101.89	11.746 / 11.556
Pulse at 15-minute (Atropine / Placebo) group A & B	61 / 79	132 / 127	100.85 / 101.93	11.494 / 11.636

Table-2: Systolic blood pressure in mmHg (SBP) variations both groups A and B. (n=72)

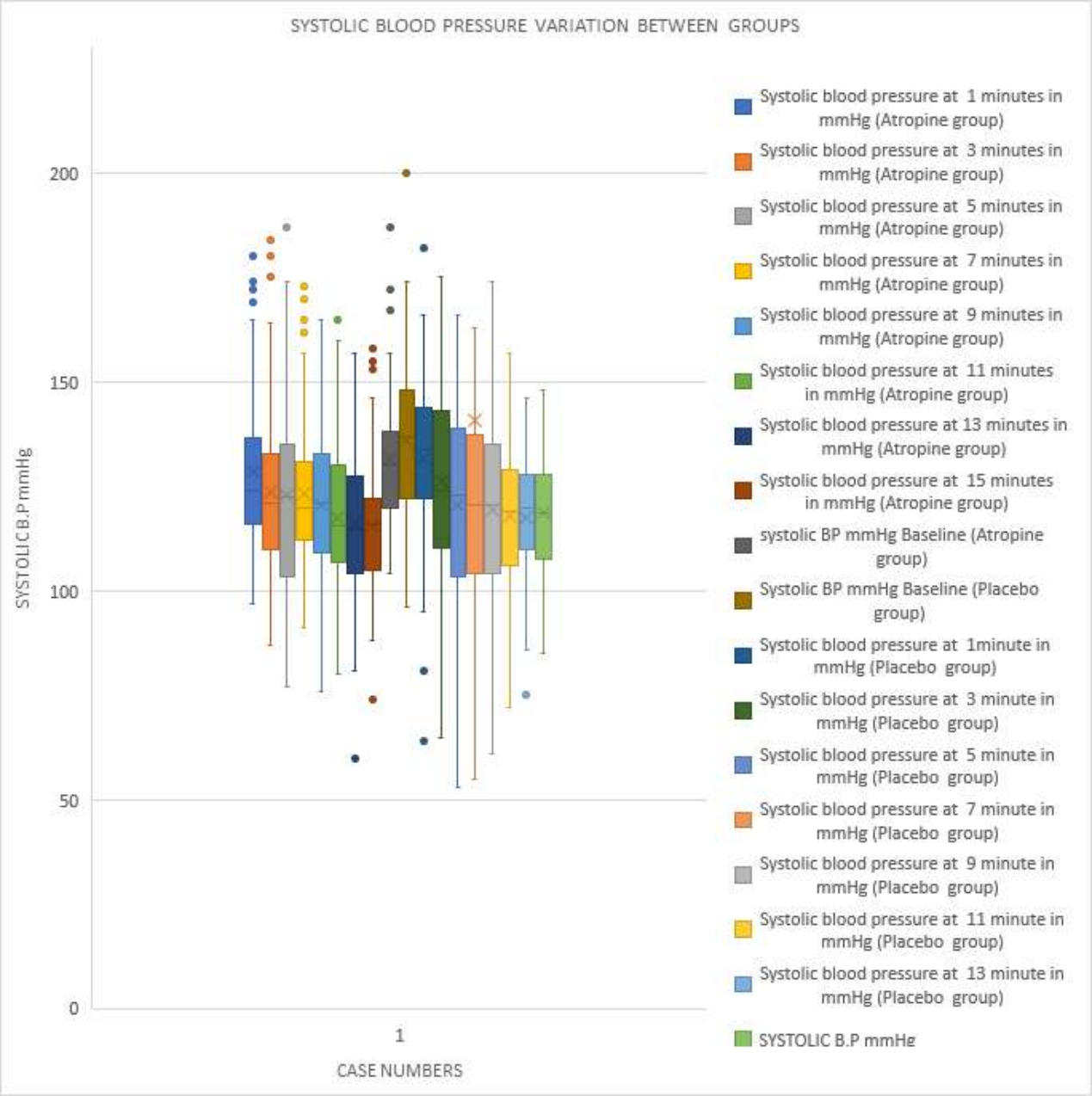
	Minimum	Maximum	Mean	Std Deviation
SBP Baseline (Atropine / Placebo) group A & B A B	104 / 96	187 / 200	131.51 / 135.74	15.260 / 18.603
SBP at, 1-minute (Atropine / Placebo) group A & B	97 / 64	180 / 182	128.62 / 131.81	18.018 / 19.703
SBP at, 3- minute (Atropine / Placebo) group A & B	87 / 65	184 / 175	123.45 / 126.16	20.082 / 22.633
SBP, at 5- minute (Atropine / Placebo) group A & B	77 / 53	188 / 166	122.75 / 120.38	24.109 / 23.381
SBP at, 7- minute (Atropine / Placebo) group A & B	91 / 55	173 / 171	123.30 / 119.40	17.834 / 22.848
SBP at, 9- minute (Atropine / Placebo) group A & B	76 / 61	165 / 174	120.51 / 119.40	18.598 / 21.734
SBP at, 11-minute (Atropine / Placebo) group A & B	80 / 72	165 / 157	117.69 / 117.90	17.703 / 18.105
SBP at,13- minute (Atropine / Placebo) group A & B	60 / 75	157 / 146	116.11 / 117.66	17.835 / 14.805
SBP at,15-minute (Atropine / Placebo) group A & B	74 / 85	158 / 148	115.45 / 118.66	15.067 / 14.733

Graph-1: Pulse variations in both groups (n=72)

A study showed using crystalloid infusion of atropine in spinal anesthesia can increase heart rate in the initial few minutes and lowers incidence of hypotension after sub-arachnoid block.[15] In another study, pinal anesthesia-induced hypotension (resulting from arterial and venous vasodilatation resulting due to the sympathetic block along with a paradoxical cardioinhibitory receptors activation) occurs frequently, particularly in the elderly and in patients undergoing caesarean spinal delivery, though several strategies have been advocated, but no one measure has been sufficiently effective and they stated that bradycardia after spinal block must be urgently treated.[16]

In another study atropine in (dose of 0.6mg) was administered one minute after placing intra-thecal block in elderly surgical

Graph-2: Systolic blood pressure variation both groups A and B (n=72)



patients and was noted to be helpful in lowering the incidence of hypotension and bradycardia.[17] In study done atropine prophylactic was administered in parturient undergoing cesarean section in a teaching hospital set-up and they supported the regimen, keeping in view better hemodynamic values noted after spinal block.[18] The results support our study inference. In look for better and newer agents, a study was done employing prophylactic nor-epinephrine along with its rescue use as required in cesarean spinal delivery and depicted promising results with prophylactic use needing less atropine and vasopressors.[19]

In study by Aweke Z and colleagues, it was rationalized to treat bradycardia and hypotension after subarachnoid block by administering atropine initially followed by if needed vasopressor agents.[20] In another study, it was concluded that atropine given prophylactically in spinal caesarean delivery had better and stable haemodynamic (pulse and blood pressure) parameters.[21] In another study, it was concluded that methoxamine along with atropine bolus administration in caesarean section under spinal anaesthesia had augmented hemodynamic effect with few adverse effects, in comparison to when methoxamine was given separately.[22]

Limitation of the study was that invasive blood pressure technique was not used, we relied on non-invasive blood

pressure readings, it was multi-centered study, emergency cases and those parturient with co-morbid diseases were not extrapolated. More randomized, case-controlled studies are required to further validate our findings.

CONCLUSION:

Prophylactic bolus of atropine against blunt unopposed vagal activity provided stable hemodynamic (pulse and systolic blood pressure) values in caesarean section at time of spinal block.

Authors Contribution:
Muhammad Salman Maqbool: Concept & Design Study, Drafting, Revisiting Critically, Final approval of version
Shumaila Ashfaq: Concept & Design Study, Drafting, Revisiting Critically, Data Analysis

1. Sugo Y, Kubota M, Niwa H, Hirota K. Moderate rate of implementation of spinal anesthesia for cesarean section: does it improve neonatal well-being? A case–-control study. Sci Rep 2021; 11:245. https://doi.org/10.1038/s41598-020-80666-7
2. Kim WH, Hur M, Park SK, Yoo S, Lim T, Yoon HK, Kim JT, Bahk JH. Comparison between general, spinal, epidural, and combined spinal-epidural anesthesia for cesarean delivery: a network meta-analysis. Int J Obstet Anesth. 2019; 37:5-15. https://doi.org/ 10.1016/j.ijoa.2018.09.012
3. Khan ZH, Eftekhar N, Barrak RS. General versus Spinal Anesthesia During Caesarean Section: A Narrative Review. Arch Anesth Crit Care 2019; 5(1): 18-21. https://doi.org/10.18502/aacc.v5i1.743
4. Sklebar I, Bujas T, Habek D. Spinal anaesthesia-induced hypotension in obstetrics: prevention and therapy. Acta Clin Croat. 2019;58(1):90–95.
5. Rattenberry W, Hertling A, Erskine R. Spinal anaesthesia for ambulatory surgery. BJA Educ.2019;19(10):321-28. DOI: https://doi.org/10.1016/j.bjae.2019.06.001
6. Alegbeleye BJ. Sudden cardiac arrest under spinal anesthesia in a mission hospital: a case report and review of the literature. J Med Case Reports. 2018; 12:144. https://doi.org/10.1186/s13256-018-1648-5.
7. Gelaw M, Haddis L, Abrar M, Aregawi A, Melese E. Effects of prophylactic atropine in prevention of spinal anesthesia induced hypotension and bradycardia in geriatrics undergoing urological surgeries at a resource limited setting in Central Ethiopia Int. J. Surg. Open 2018; prospective cohort study. 2020; 26:42- 48. https://doi.org/10.1016/j.ijso.2020.08.004
8. Akhtar FM, Pirzada A, Ashraf V. Prevention of hypotension in caesarean delivery under spinal anaesthesia; the combination of modified supine wedged position, crystalloid cohydration and prophylactic atropine. PAFMJ 2008;58(4):429-36. https://pafmj.org /index.php/PAFMJ/article/view/1965
9. Butterworth IV JF, Mackey DC, Wasnick JD. Morgan & Mikhail Clinical Anesthesiology. 5th Edition. Appleton and Lange 2013; 10: 189-98.
10. Sigdel S. Prophylactic use of IV atropine for prevention of spinal anesthesia induced hypotension and bradycardia in elderly: a randomized controlled trial.J Anesthesiol Clin Sci. 2015; 4:5. https://doi.org/10.7243/2049-9752-4-5
11. Arya S, Belwal S, Uniyal B, Tiwari B, Sharma P. Bezold Jarisch Reflex- New Interest, Old Phenomenon, Am J Intern Med. 2020;8(1):24-29. https://doi.org/ 10.11648/j.ajim.20200801.15
12. Limongi JA, Lins RS. Cardiopulmonary Arrest in Spinal Anesthesia. Rev Bras Anestesiol 2011;61(1):110-20. https://doi.org/10.1016/S0034-7094(11)70012-5
13. Maqbool MS. Evaluation of Heart Rate Variability and Baroreflex Sensitivity in Cesarean Spinal Delivery. Med Forum 2018;29(3):78-82.
14. Warltier DC, Campagna JA, Carter C. Clinical Relevance of the Bezold–Jarisch Reflex. Anesthesiology 2003; 98:1250–1260. DOI:10.1097/00000542-200305000-00030.
15. Lim HH, Ho KM, Choi WY, Teoh GS, Chiu KY. The use of intravenous atropine after a saline infusion in the prevention of spinal anesthesia-induced hypotension in elderly patients. Anesth Analg. 2000;91(5):1203-6. DOI: 10.1097/00000539-200011000-00029.
16. Ferre F, Martin C, Bosch L, Kurrek M, Lairez O, Minville V. Control of Spinal Anesthesia-Induced Hypotension in Adults. Local Reg Anesth. 2020; 13:39-46. DOI: 10.2147/LRA.S240753
17. Lakshmi Vanaja N. Comparison of Atropine with Ephedrine in Prevention of Spinal Anesthesia Induced Hypotension in Elderly Age Group. Indian J Anesth Analg. 2019; 6:1973-77. DOI: http://dx.doi.org/10. 21088/ijaa.2349.8471.6619.16
18. Nze PU. Effect of pre-medication with atropine on the blood pressure of parturient undergoing caesarian section under spinal anaesthesia. Orient Journal of Medicine. 2003;15(1):1-4. DOI: 10.4314/ojm. v15i1.29037
19. 19.Xu T, Zheng J, An XH, Xu ZF, Wang F. Norepinephrine intravenous prophylactic bolus versus rescue bolus to prevent and treat maternal hypotension after combined spinal and epidural anesthesia during cesarean delivery: a sequential dose-finding study Ann Transl Med 2019;7(18): 451.DOI:org/10.21037/atm.2019.08.50
20. Aweke, Z., Mola, S., Solomon, F.E., Ayalew, N., Hailu, S., Neme, D et al. Prophylactic efficacy of intravenous atropine with crystalloid co-loading for hemodynamic stability in parturient undergoing cesarean delivery at Dilla University Referral Hospital. A randomized controlled trial. Int. J. Surg. Open.2021;30(2): 100321.DOI: 10.1016/j.ijso.2021.100321
21. Nze PUN. Effect of pre-medication with atropine on the blood pressure of parturient undergoing caesarian section under spinal anaesthesia. Orient J Med. 2003;15(1):1-4. DOI: 10.4314/ojm. v15i1.29037
22. Luo XJ, Zheng M, Tian G, Zhong HY, Zou XJ, Jian DL. Comparison of the treatment effects of methoxamine and combining methoxamine with atropine infusion to maintain blood pressure during spinal anesthesia for cesarean delivery: a double blind randomized trial. Eur Rev Med Pharmacol Sci. 2016;20(3):561-567. PMID: 26914134

Original Article **Open Access**

Anthropometric Measurements for Determination of Occlusal Vertical Dimension in Relation to Eye

Pooja Kumari, Sajida Khuhawar, Muhammad Rizwan Memon, Madiha Khalid Memon, Naresh Kumar, Priya Rani Harjani

ABSTRACT

Objective: To determine the mean vertical dimension of occlusion among dentate population by using different anthropometric measurements in relation to eye.

Study Design and Setting: It was a cross sectional study conducted at outpatient department of prosthodontics, Liaquat University of Medical and Health Sciences, Jamshoro from March –Sep-2019.

Methodology: Five eye characteristics were measured. The distance between the outer canthus of one eye and the inner canthus of the opposite eye is measured in millimeters, outer canthus to rima oris distance, interpupillary distance, mid pupil to rima oris distance and canthus to tragus distance. Data were analyzed using SPSS Version 20. Mean and SD for age distinction between right and left pupil, rima oris and tragus. The outcome was assessed using age and gender stratification. The age and gender groups were compared using a t -test.

Results: Total n=100 patients with complete dentitition were included for data collection. Mean age was 22.75±1.86 years. Mean vertical dimension of occlusion (OVD) among dentate population was 67.73±1.02 mm. The mean inter canthus distance was 63.13±2.95mm, the mean interpupillary distance was 61.21±1.67mm, rima oris to pupil was 67.46±1.53mm and eye to ear distance was 70.04±1.68mm

Conclusion: The OVD index identifies the precise vertical dimensions as being present in dentate populations. This index could be used in clinical setting before using other methods to estimate vertical dimension to provide a general sense of the patient's vertical dimension.

Keywords: Anthropometric measurements, Dentate, Freeway Space, Occlusal Vertical Dimension-OVD, Vertical dimension

How to cite this Article:
Kumar P, Khuhawar S, Memon MR, Kumar N, Harjani PR. Anthropometric Measurements for Determination of Occlusal Vertical Dimension in Relation to Eye. J Bahria Uni Med Dental Coll. 2022; 11(3):124-128 DOI: https://doi.org/10.51985/JBUMDC202188

Pooja Kumari
FCPS Resident, Department of Prosthodontics
Liaquat University of Medical & Health Sciences, Jamshoro
Email: poojakumari9275@gmail.com

Sajida Khuhawar
Lecturer Department of Science of Dental Materials
Liaquat University of Medical & Health Sciences, Jamshoro
Email: sajda_khuhawar@yahoo.com

Muhammad Rizwan Memon
Professor Department of Prosthodontics
Liaquat University of Medical & Health Sciences, Jamshoro
Email: Muhammad.rizwan@lumhs.edu.pk

Madiha Khalid Memon
Assistant Professor Department of Oral Biology
Muhammad Medical & Dental College, Mirpurkhas
Email: Laila31dec@gmail.com

Naresh Kumar
Assistant Professor Department of Operative Dentistry & Endodontics
Bhittai Dental & Medical College, Mirpurkhas
Email: naresh_jes392@yahoo.com

Priya Rani Harjani
Lecturer Department of Prosthodontics
Bibi Aseefa Dental College, Larkana
Email: priya.harjani@hotmail.com

Received: 21-Oct-2021
Accepted: 19-May-2022

INTRODUCTION:

Nobody wants to have their natural teeth extracted and then must wear a denture to replace them. However, the patient's anguish can be alleviated to some extent by providing an artificial tooth that looks and functions like natural teeth. The vertical dimension of occlusion decreases in proportion to tooth loss, which is defined as the distance between two anatomic locations, usually one at each end of the nose and one at the base of the chin, one of which is fixed and the other of which is movable.[1] The patient's ability to speak and chew effectively, as well as their appearance, are compromised because of a reduction in lower facial height. The disease has a negative psychological and social impact on the person.[2]

One of the most important aspects of successful prosthodontic therapy is determining the optimal vertical dimension of occlusion. Premature tooth contacts, in the absence of proper occlusal vertical dimension (OVD), can cause increased stress to the underlying tissues, as well as other consequences such as muscular tiredness and a full mouth, among others. Reduced biting force and problems with the temporomandibular joint are all symptoms of senility if this is not maintained.[2-4]

Numerous methods are available to determine the vertical dimension of occlusion, including pre-extraction records, physiological rest posture and swallowing tests, phonetics, aesthetic and cephalometric radiographs, and facial measurements, but none of these methods are completely reliable.[5] Cephalometric measurements could improve OVD reliability. OVD could be determined by measuring the lower face height angle (anterior nasal spine-Xi protuberance menti). An ideal OVD could be saved in the patient's virtual file for the rest of their lives, making dento-maxillary rehabilitation much easier and more predictable.[6] Prior research by Bishal Babu discovered that when measuring the distance between the rima oris and pupil of one eye, the mean vertical occlusion dimension was 69.324.17 mm, and that this measurement could be used in conjunction with the rima oris-to-pupil distance to determine the vertical occlusion dimension.[7] Lindawati S Kusdhanyet al discovered that the mean interpupillary distance was 62.253.27 mm and this value could be used to calculate the vertical occlusion dimension.[8]

People of different races or ethnicities may not be able to use the same types of measurements when measuring their faces. Even people of the same race living in different parts of the world can appear to be different in appearance. Racial and socio-cultural factors have a direct impact on communication ability.[9] In order to gather information, the purpose of this study was to determine the occlusal vertical dimension in the dentate population by comparing different anatomical measures to the local population's eye measurements. Because no two people are the same height or width, measurements will vary from one group to the other. The study's findings will be useful in determining how much occlusal vertical dimension an edentulous patient has lost. These figures will be useful for general dentists who, as these figures show, can easily implement these approaches without the use of any complex instruments. Hence, this study was aimed to determine mean vertical dimension of occlusion among dentate population by using different anthropometric measurements in relation to eye.

METHODOLOGY:

This cross-sectional study with consecutive sampling technique was conducted at Outpatient Department of Prosthodontics at Liaquat University of Medical and Health Sciences in Jamshoro from March to Sep-2019. Using the WHO sample size calculator, the sample size was calculated as Inter Pupillary distance (p-p): 6.253.27 with a 95 percent confidence interval and 0.01 absolute precision. The calculated sample size was 42 subjects, but it was increased to 100 subjects. The study was approved by the ethical council with the reference number CPSP/REU/DSG-2016-166-1779 on July 6, 2020. We sought written informed consent from dentate volunteers who were willing to participate. The presence of the patient's entire dentition, Angle's Class 1 maxillo-mandibular relationship with a normal overjet of 2 to 4 millimeters and an overbite, and an age limit of 20 to 25 years for either gender were the inclusion criteria. If a subject had any orofacial or skeletal abnormalities, had previously restorative or prosthetically treated teeth, had previously undergone orthodontic treatment, had bruxism, or had tooth attrition, patients with eye squint, nystagmus and having contact lenses were all excluded from the study. They were given a thorough medical history and clinical examination, and measurements were taken on fully dentate volunteers with their teeth in contact while sitting erect and gazing forward with their heads without any support, and the occlusal plane was parallel to the floor, as described above. The vernier caliper was used to measure the vertical dimension of the occlusion as well as five anthropometric eye characteristics: millimeters between the outer canthus of one eye and the inner canthus of the opposite eye; all of these parameters were measured in millimeters three times and the results were entered into the proforma.

Following the collection of data, analyses were performed using the Statistical Package for Social Science (SPSS) software, Version 20. A mean and standard deviation were assigned to age. Gender and age were calculated as a percentage and as a frequency. To determine the effect of age and gender on the outcome, a stratification analysis was performed. The ANOVA test was used to compare outcome age groups and gender. The level of significance was set at p 0.05.

RESULTS:

This study included 100 patients who had all their teeth retained. The participants' average age was 22.75 years, with a standard deviation of 1.86 years. Men constituted 40% of the group, while women constituted 60%. In the dentate population, the mean vertical dimension of occlusion was 67.73, with a standard deviation of 1.02. The mean intercanthus distance was 63.13±2.95mm, the mean interpupillary distance was 61.21.16mm, the pupil to rima oris distance was 67.46±1.53mm, and the canthus to tragus distance was 70.041±68mm, according to Table 1. Stratification analysis was performed, and the results were presented in terms of mean comparison of vertical dimension of occlusion among dentate population by using different anthropometric measurements in relation to eye among and genders, as shown in Tables 2.

DISCUSSION:

When the vertical dimension of occlusion is restored, it not only allows artificial teeth to be placed between the top and bottom ridges, but it also improves the function of the denture prosthesis as well as the patient's aesthetic appearance. When this critical component is restored, it is critical that the patient does not experience any discomfort or tightness in the face. The measurement of the lower third of the face's vertical height is arbitrary because there are no pre-extraction records for the OVD. The average participant age in the

Table 1: Mean vertical dimension of occlusion among dentate population by using different anthropometric measurements in relation to eye

Measurements	mean±SD
Vertical dimension of occlusion (mm)	67.73±1.02
Intercanthus Distance (mm)	63.13±2.95
Interpupillary Distance (mm)	61.21±1.67
Pupil to rima oris distance (mm)	67.46±1.53
Ear – eye distance (mm)	70.04±1.68

Table 2: Stratification of vertical dimension of occlusion values in relation to gender

Measurements	Gender		P-Value
	Male	Female	
VDO (mm)	67.70±0.91	67.76±1.09	0.767
Inter Canthus Distance (mm)	63.32±1.28	62.94±3.98	0.522
Interpupillary Distance (mm)	61.04±1.76	60.96±1.60	0.813
Pupil to Rima Oris distance (mm)	67.82±1.47	67.10±1.51	0.018
Ear – eye distance (mm)	70.16±1.46	69.92±1.89	0.480

study was 22.751±86 years. There were 40% males and 60% females. The 63 participants in the Kusdhany et al study had an average age of 28 years, with 34 females and 29 men making up the sample. Before extraction treatments are performed, it is assumed that a patient's oral volume during dentation will be of the optimal dimension in terms of both aesthetics and function. A variety of treatments were recommended to maintain the pre-extraction OVD and transfer it to consecutive dentures. Internal measures, profile tracings, cephalometric tracers, and pre-extraction phonetics are just a few of the procedures used to prepare for extraction as the primary method of preparation. Only patients with an appropriate OVD and a stable occlusion can be measured using these procedures.

According to the Glossary of Prosthodontic Terms, the mandibular rest position is achieved when the head is erect, the relevant muscles are in balance tonic contraction, and the condyles are neutral and unstrained. To calculate the OVD, subtract the interocclusal distance of 2-4 mm from the mandibular rest position. Two dots on the skin's least movable parts register the mandible's resting position (e.g., nose and chin). Willis' gauge, a spring divider (caliper), a mil-ruler, and a digital caliper are also suggested. Phonetics is a popular treatment method in which the patient is instructed to pronounce the labial 'M' without tensing their lips when speaking. If the patient's lips remain parted after making the 'M' sound, certain issues may arise. To avoid this problem, many terms (Emma, Mississippi) have been recommended to keep the jaw relaxed and the mouth parted. During the second procedure, you must relax your jaw. Exercises can help the patient learn how to swallow and hold their mandible properly. The third method is called "no command" or "relaxation" when a patient is asked to relax and keep their mandible in a comfortable position. In clinical practice, these techniques are frequently used in tandem to rest the mandible. Bishal babu[7] concluded in previous literature that the mean Inter Canthus distance was 66.993±73 mm, pupil to rima oris distance was 64.774±65 mm, and ear eye distance was(69.324±17 mm, which can be used to determine vertical dimension of occlusion. Lindawati S Kusdhanyet al[8] concluded in another study that the mean inter pupillary distance was 62.253±27), which can be used to calculate VDO.

Hayakawa also created a model for predicting vertical dimension of the sn-gn distance, which was used. Hayakawa projected the vertical dimension based on the pupil-chelion distance (p-ch). The inter pupillary distance (p-p) measurement and the participant's gender were used to predict the occlusal vertical dimension in this study. In this study, researchers were able to precisely determine the occlusal vertical dimension by measuring the inter pupillary distance (p-p), which they discovered during their research. The data support the assumption that differences in outcomes are related to differences in profile between races.[11-12]

McGee[13] used anthropometric data to determine the relationship between OVD and other factors. According to their findings, original OVD is frequently equivalent to intercanthus distance, ear height, double length of one eye, interpupillary distance, and nose midline. In other studies, the differences between OVD and finger length ranged from 2-4 mm, indicating that this method of OVD prediction is accurate and repeatable.[14]

Dentists most commonly use visual observations of the gap between the mandibular rims in their physiologic rest posture (freeway space), aesthetic judgement, and phonic tests, which include observations when the "s" sound is recurrently enunciated, among other techniques, to establish accurate OVD in clinical practice. The OVD is assessed based on aesthetic harmony in the lower face. An ideal OVD has a relaxed face with slightly pressed lips. If the lower region of the face is squeezed, the OVD has progressed too far. When the OVD is lowered, however, the corners of the mouth may recede. This method can be used to assess OVD in patients who are young or middle-aged and have normal skin tonus. This method may not produce an ideal OCD if this tone is lost, or the lips are insufficient. While facial aesthetics are frequently used in conjunction with various methods for creating OVD, their ability to distinguish between incremental changes in OVD when used by the dentist or the patient is limited. The OVD index will be used to validate alternative techniques.[15-17] According to Nepalese anthropometric research, the distance between the rima oris and the pupil has a stronger association with OVD than any other facial measurement.[7] Several studies have linked OVD and finger anthropometry.[18-20]

Getting the right OVD is critical because an excessive inter-

arch distance when the patient is in occlusion prevents his or her lips from softly contacting each other when the patient is relaxed. The patient may appear to be extending his or her bottom lip to make contact. The muscles responsible for elevating the lower jaw are unable to fully contract due to the limited amount of available space. These muscles will continue to work hard to overcome this obstacle. In many cases, this causes damage to the supporting tissues, resulting in symptoms such as discomfort, possible ischemia, and, eventually, resorption. When a patient has difficulty closing their lips properly due to excessive OVD, this can lead to facial deformity.[21] An excessive interocclusal distance, on the other hand, can cause complications. Increased OVD during tooth contact can cause TMJ damage, facial distortion, muscle atrophy, and possibly angular cheilitis (angular cheilitis). Numerous studies have recommended a freeway of 2 mm to 4 mm as a standard. Dentures have long used this method of measuring vertical dimension by highway space. When driving on freeways, keep in mind that the area is only used to repair denture teeth and install models for the try-in procedure.[22] Phonetics and aesthetics are used during the try-in to fine-tune the final incisal edge placement, which is then recorded. There is no single correct vertical dimension because of the numerous different approaches to determining vertical dimension that have been investigated. As a result, we can conclude that the vertical dimension is highly variable.[23-25] The OVD index can be used in two ways: before or after other procedures to assess the patient's vertical dimension, or after the results of those other procedures to validate the results of those other procedures.

CONCLUSION:

The OVD index identifies the precise vertical dimensions as being present in dentate populations. This index could be used in clinical setting before using other methods to estimate vertical dimension to provide a general sense of the patient's vertical dimension.

Authors Contribution:
Pooja Kumari: Study Design & Data Collection
Sajida Khuwar: Study Design, Manuscript Writing
Muhammad Rizwan Memon: Literature Review, Data Analysis and Research Monitoring
Madiha Khalid Memon: Study Design & Data Interpretation
Naresh Kumar: Literature Review, Data Analysis and Research Monitoring
Priya Rani Harjani: Manuscript Writing, Statistical Analysis

REFERENCES:

1. Alhajj MN, Khalifa N, Abduo J, Amran AG, Ismail IA. Determination of occlusal vertical dimension for complete dentures patients: an updated review. J Oral Rehabil. 2017;44(11):896–907. DOI: https://doi.org/10.1111/joor.12522
2. Alves AC, Cavalcanti RV, Calderon PS, Pernambuco L, Alchieri JC. Quality of life related to complete denture. Acta Odontol Latinoam. 2018;31(2):91–6.
3. Discacciati JAC, Lemos de Souza E, Vasconcellos WA, Costa SC, Barros V de M. Increased vertical dimension of occlusion: signs, symptoms, diagnosis, treatment and options. J Contemp Dent Pract. 2013;14(1):123–8. DOI: https://doi.org/10.5005/jp-journals-10024-1284
4. Sambataro S, Cervino G, Bocchieri S, Bruna R La, Cicciù M. TMJ dysfunctions systemic implications and postural assessments: A review of recent literature. J Funct Morphol Kinesiol. 2019;4(3). DOI: https://doi.org/10.3390/jfmk4030058
5. Bajunaid SO, Baras B, Alhathlol N, Ghamdi A Al. Evaluating the Reliability of Facial and Hand Measurements in Determining the Vertical Dimension of Occlusion. Int J Med Pharm. 2017;5(1):1–11. DOI: https://doi.org/10.15640/ ijmp .v5n1a1
6. Oancea L, Burlibasa M, Petre AE, Panaitescu E, Cristache CM. Predictive model for occlusal vertical dimension determination and digital preservation with three-dimensional facial scanning. Appl Sci. 2020;10(21):1–15. DOI: https://doi.org/10.3390/app10217890
7. Babu Basnet B, Kumar Singh R, Kumar Parajuli P, Shrestha P. Correlation between Facial Measurements and Occlusal Vertical Dimension: An Anthropometric Study in Two Ethnic Groups of Nepal. Int J Dent Sci Res. 2014;2(6):171–4. DOI: https://doi.org/10.12691/ijdsr-2-6-13
8. Kusdhany LS, Indrasari M, Koesmaningati H, Leepel MB, Oktaria I. Occlusal vertical dimension index to simplified vertical dimension measurement. 2016;9(Special Issue):334–8.
9. Muhammad Irfan M, Muhammad A MK. Determination of occlusal vertical dimension in a section of Pakistani population using craniofacial measurements. J Univ Med Dent Coll. 2015;6(1):1–5.
10. Akhma NE, Sumarsongko T, Rikmasari R. Correlation between the occlusal vertical dimension and the pupil rima oris distance among Sundanese population. Padjadjaran J Dent. 2017;29(2). DOI: https://doi.org/10.24198/pjd.vol29no2.13657
11. Park DH, Choi WS, Yoon SH, Song CH. Anthropometry of asian eyelids by age. Plast Reconstr Surg. 2008;121(4): 1405–13. DOI: https://doi.org/10. 1097/01.prs. 0000304608. 33432.67
12. Majeed MI, Haralur SB, Khan MF, Al Ahmari MA, Al Shahrani NF, Shaik S. An anthropometric study of cranio-facial measurements and their correlation with vertical dimension of occlusion among Saudi Arabian subpopulations. Open Access Maced J Med Sci. 2018;6(4):680–6. DOI: https:// doi.org/10.3889/oamjms.2018.082
13. McGEE GF. Use of facial measurements in determining vertical dimension. J Am Dent Assoc. 1947 Sep;35(5):342–50. DOI: https://doi.org/10.14219/jada.archive.1947.0361
14. Hajimahmoudi M, Bahrami M, Nozarpoor S. Comparative Evaluation of the Inter-Occlusal-Distance and Closest Speaking Space in Different Angle's Occlusion Classes. Dent Adv Res. 2018;5(2). DOI: https://doi.org/10.29011/2574-7347.100050
15. Ajay R, Manoharan PS, Rakshagan V, OmarFarooq BM, Arunkumar P, Sasikala R. Correlation of Vertical Dimension of Occlusion in Parents and Their Offspring: A Cephalometric Study. J Pharm Bioallied Sci. 2019; 11(Suppl 2): S371–5. DOI: https://doi.org/10.4103/jpbs.jpbs_37_19

16. Geerts GAVM, Stuhlinger ME, Nel DG. A comparison of the accuracy of two methods used by pre-doctoral students to measure vertical dimension. J Prosthet Dent. 2004; 91(1):59–66. DOI: https://doi.org/10.1016/j. prosdent. 2003.10.016

17. Calamita M, Coachman C, Sesma N, Kois J. Occlusal vertical dimension: treatment planning decisions and management considerations. Int J Esthet Dent. 2019;14(2):166–81.

18. Aziz Miran F, Ahmed Mahmood BDS K. The Correlation between the Right Little Finger, Eye -Ear Distance and Vertical Dimension of Occlusion among Students of Faculty of Medical Sciences in University of Sulaymani. IOSR J Dent Med Sci Ver I [Internet]. 2015;14(12):2279–861. Available from: www.iosrjournals.org

19. Bhandari Aruna J, Ladda R, Bhandari Akshay J. Correlation between vertical dimension of occlusion and length of little finger. Pravara Med Rev. 2012;4(4):10–4.

20. Saad M, Munshi M, Shah MU, Shaikh MI. Role of Anthropometric Measurements in Determining Occlusal Vertical Dimension. 2020;40(2):103–6.

21. Chou JC, Thompson GA, Aggarwal HA, Bosio JA, Irelan JP. Effect of occlusal vertical dimension on lip positions at smile. J Prosthet Dent. 2014;112(3):533–9. DOI: https://doi.org /10.1016 /j.prosdent.2014.04.009

22. Preston AJ. Removable Prostheses Revisited: Challenges for Primary Dental Care. 1. Complete Dentures. Prim Dent Care. 2007;os14(2):67–72. Available from: https://doi.org/10.1308/135576107780556680

23. Abduo J, Lyons K. Clinical considerations for increasing occlusal vertical dimension: a review. Aust Dent J. 2012; 57(1):2–10. DOI: https://doi.org/10.1111/j.1834-7819.2011.01640.x

24. Igiæ M, Kruniæ N, Aleksov L, Kostiæ M, Igiæ A, Petroviæ MB, et al. Determination of vertical dimension of occlusion by using the phonetic vowel “O” and “E”. Vojnosanit Pregl. 2015;72(2):123–31. DOI: https://doi.org/10.2298/vsp1502123i

25. Frank SM. Approaches to Vertical Dimension Abstract : Vertical dimension is a highly debated topic in dentistry . Differences of opinion over how. Adv Esthet Interdiscip Dent. 2006;2(3):1–14

Original Article **Open Access**

Acute Migraine Attack in Students while taking Online Classes during Pandemic

Abdul Zahir

ABSTRACT

Objectives: To determine the frequency of migraine in students taking online classes during Covid-19 pandemic.

Study design and setting: Cross-sectional study design using a non-probability convenient sampling technique was conducted and carried out for a period of three months from August 2021 to November 2021 at Bolan Medical College. Total n=500 students of secondary, high school, and undergraduate students of different disciplines attending online classes during the COVID-19 pandemic were the target population.

Methodology: The questionnaire comprised of four sections; students' demography, mean duration of using digital devices before and during the COVID-19 pandemic, and presenting to the hospital with complaints of headache/migraine. Students willing to participate were included while students that refused to participate were excluded. SPSS version 23.0 was used for data analysis. To determine the association between mean duration usage of digital devices, presenting with headache/migraine or the use of glasses in-between pre-COVID and COVID era, a one-sample t-test was applied keeping p-<0.05 statistically significant.

Results: From 500 students, the mean age was 18 ± 3.2 years. There were n=274 (54.8%) males and n=226 (45.2%) females. The mean duration of using digital devices in the pre-COVID era were 1.8 ± 0.7 hours while in the COVID era were 3.6 ± 1.9 hours. A significant difference was observed in terms of mean duration of digital device usage, frequency of migraine and use of glasses in COVID-19 era when compared with pre-COVID era.

Conclusion: Increase in use of digital devices during COVID-19 pandemic caused increased complains of headache/migraine among the students. Additionally majority of students reported decrease in visual acuity during the pandemic due to which they had to wear glasses.

Keywords: COVID-19, Headache, Migraine, Online classes, Stress.

How to cite this Article:
Zahir A. Acute Migraine Attack in Students while taking Online Classes during Pandemic . J Bahria Uni Med Dental Coll. 2022; 11(3): 129-132 DOI: https://doi.org/10.51985/JBUMDC2021116

INTRODUCTION:

Migraine is a common, chronic, debilitating neurovascular disorder, which is characterized by recurrent attacks of severe headache and dysfunction of autonomic nervous system.[1] It is unilateral and throbbing in nature, frequently associated with a variety of other non-specific symptoms such as nausea, vomiting, photophobia, and phonophobia.[2] Migraine attacks can last up to 4-72 hours and are diagnosed based on a combination of features. However, not all features must be present in every spell, and may differ from patient to patient.[3]

Worldwide, an acute headache disorder are estimated at about 46%, according to International Headache Society criteria for migraine and tension-type headache. Migraine is 11%, tension-type headache is 46% and chronic daily headache is 3%.[4] The reported values revealed that headache disorders are causing disability in patients' daily routine lives on a global scale. According to WHO, such figures would make migraine the most disabling condition for both genders.[5] Preventive therapy may decrease the frequency of migraine attacks by up to 50% or more. To diagnose and evaluate the patient diagnostic screening is important.[6]

Digital device usage has been linked with increased frequency of migraine attack. The extensive use of computer as medium of teaching and learning in universities required self-analysis into the extent of computer related health disorders among students population.[7] Constant exposure to internet creates negative impact on life and imparts serious health issues like chronic fatigue, altered sleep, visual problem, migraine and low immunity.[8] The severity of internet addiction is associated with severity of headache. Since the beginning of the pandemic in 2020, the COVID-19 virus impaired the global health care system and all aspect of human's life as well. All educational institution remains closed worldwide and had to switch towards online, e-learning systems [9]. The pandemic affected student's social and educational academic life. They are concerned about their academic career. To

Abdul Zahir
Senior Registrar Department of General Medicine
Post Graduate Medical Institute Quetta
Email: abdul.zahir@ yahoo.com

Received: 09-Dec-2021
Accepted: 19-Jun-2022

diminish these issues educational sectors introduced online learning strategies. Prolong sessions in front of computer, laptop and mobile for online classes' students may get serious health issues and migraine is one of them.[10]

Thus, the objective of study was to determine the frequency of migraine in students taking online classes during the Covid-19 pandemic.

METHODOLOGY:

This cross-sectional observational study using a non-probability convenient sampling technique was carried out for a period of three months from August 2021 to November 2021 at Bolan Medical College. The study was done after approval from the Institutional Review Committee. The ERC was issued with ERC number-PGMI-2958. This was a questionnaire-based quantitative study only among students of secondary, high school and undergraduate students who were attending classes online during the COVID-19 pandemic. The sample size was calculated by using openepi software with 95 % confidence level and 50 % anticipated frequency, the sample size came out to be 385. But this study included 500 students as during the time period for data collection, 23 % more students agreed for participation in the study.

The questionnaire was comprised of four sections; students' demography, the mean duration of using digital devices before and during the COVID-19 pandemic, and presenting to the emergency department or medical out-patient department with a complaint of headache/migraine as a presenting symptom. Furthermore, questions were asked regarding the use of glasses before the COVID-19 pandemic and if glasses were used during the pandemic (for exclusion criteria). Regarding examination, the visual acuity of each study participant was checked by taking the participants to the ophthalmologist. Prior to student's recruitment, they were informed regarding the duration, purpose and anonymity of the research. Students willing to participate in the study were included in the study while those students that refused to participate in the study were excluded. For determining the average time a student spent on digital devices, it was asked from parents as well (not for confirming the answer given by the students). No other question was asked from the parents nor was any other questionnaire used. Digital devices included computers, smartphone, and any other digital device used during COVID-19 pandemic for taking online classes.

For diagnosing headache/migraine, the criterion of International Headache Society was used i.e., A. At-least five episodes fulfilling criteria B-D has occurred. B. Headache lasting 4-72 hours (untreated or unsuccessfully treated) C. Headache with at-least two of the following characteristics; unilateral location, pulsating nature, moderate to severe pain intensity, aggravating or causing avoidance of routine physical activities, during headache with at-least one of the following i.e., nausea and vomiting, photophobia, photophobia, headache is not attached to another disorder.[11]

SPSS version 23.0 was used for data analysis. For descriptive data, frequency and percentages were reported while for quantitative data; mean and standard deviation were reported. For determining the association between mean duration usages of digital devices, presenting with headache/migraine as a symptom or the use of glasses in-between pre-COVID and COVID era, one-sample t-test was applied keeping p-value of <0.05 as statistically significant.

RESULTS:

Total of 500 students included in the study with mean age of 18 ± 3.2 years. The frequency of males was n=274 (54.8%) and females was n=226 (45.2%). Total n=270 (54%) of students were undergraduate students, n=122 (24.4%) of students were high school students while n=108 (21.6%) of students belonged to secondary schools. The mean duration of using digital devices (mobile, computers, television, laptop/notebook) in the pre-COVID era were 1.8 ± 0.7 hours with n=422 (84.4%) students. The mean duration of using digital devices (mobile, computers, television, laptop/notebook) in the COVID era were 3.6 ± 1.9 hours with n=64 (12.8%) students spending time on digital devices for <3 hours per day and n=436 (87.2%) of students spending >3 hours per day=graph-I. All the included students, i.e. 500 attended online classes and presented with headache/migraine as a presenting complaint. Prior to COVID pandemic, 104 (20.8%) students used spectacles, however during the COVID era, 290 (58.0%) of students used spectacles. A 6/6 to 6/12 visual acuity was observed in 120 (24%) of students, 6/12 to 6/18 in 250 (50%) of students while <6/18 was observed in 130 (25%) of students (Table I)

The mean duration of digital devices usage in the pre-COVID and COVID era showed significant difference with P-Value <0.001. Students experiencing headache/migraine in pre-COVID era was in around n=104 (20.8%) of students while in the COVID era, all students included in the study presented with headache/migraine as a presenting symptom, with p-value of <0.0001. The use of glasses in pre-COVID era, 104 (20.8%) and in the COVID era, 290 (58%) showed a significant difference of <0.001 [Table II].

DISCUSSION:

According to the study results, a significant increase in the frequency of headache / migraine along with the use of glasses was reported (p<0.0001 and p<0.001) in the COVID-19 era when compared with the pre-COVID period. The mean duration of digital device usage increased from 1.8 ± 0.7 hours/day to 3.6 ± 1.9 hours / day.

In accordance with our study reported, a study reported an increased frequency of headache/migraine amongst students that spent more time on digital device usage.[12] Similarly

Table I: Baseline demographics of patients included in the study (n=500)

Variables		Frequency	%
Mean age (years)		18	± 3.2
Gender	Male	274	54.8
	Female	226	45.2
Class	Secondary	108	21.6
	High school	122	24.4
	Undergraduate	270	54.0
Mean duration of using digital devices (pre-COVID)		1.8	± 0.7
<3 hours		422	84.4
>3 hours		78	15.6
Mean duration of using digital devices (COVID era)		3.6	± 1.9
<3 hours		64	12.8
>3 hours		436	87.2
Online classes attended		500	100
Presenting with headache/migraine as symptom		500	100
Use of glasses before COVID	Yes	104	20.8
	No	396	79.2
Use of glasses in COVID era	Yes	290	58.0
	No	210	42.0
Visual Acuity	6/6 to 6/12	120	24.0
	6/12 to 6/18	250	50.0
	<6/18	130	25.0

Figure: 1 Graphical representation of duration of digital device usage in COVID era (n=500)

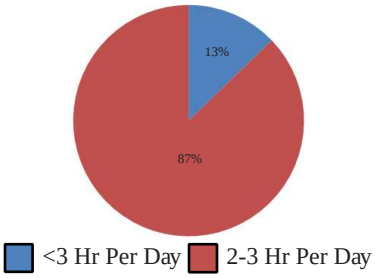


Table II: Association of various factors in online learning / use of digital devices with factors associated with headache/migraine

Variables	Pre-COVID era	COVID era	p-value
Mean duration of using digital devices (hours)	1.8 ± 0.7	3.6 ± 1.9	<0.001
Presenting with headache/migraine as symptom	104 (20.8 %)	500 (100 %)	<0.0001
Use of glasses	104 (20.8 %)	290 (58 %)	<0.001

another research also observed that the use of digital devices especially for long duration online classes were significantly associated with decrease in vision as well as increased frequency of headache/ migraine. Probably the reason of higher prevalence in undergraduate students would be having multiple factors such as increased level of stress associated with academic and economic burden, lack of sleep, improper diet and limited or lack of physical activities. These factors may increase due to more burden and responsibilities on them [13, 14]. In yet another study to determine the screen time-exposure and reporting of headache in young adults, the results of the study suggested that the students with the highest screen time exposure reported an increased risk of migraine. The results of this study proved that long duration use of digital devices could possibly provoke headache.[15]

Similar to this study, another study conducted during the COVID-19 pandemic found similar effects on student's mental health in terms of increased frequency of headache/ migraine coupled with visual impairments such as decrease in visual acuity, refractive errors etc.[16, 17]

Likewise in yet another research in which 46 students with mean age of 14.46 years were included with a mean duration of online classes at 3.08 ± 1.68 hours observed an increase of stressful symptoms such as headache/migraine, visual impairments and distress.[18]

In accordance with the findings of this study where due to increased screen time led to higher rates of migraine, published literature suggests that firstly screen time is referred to as the time duration which is spent in activities involving pairing with a digital screen, such as computer, laptop, tablet, mobile phones etc. Not only for online learning/classes, but screen time has increased in the pandemic for other services as well. Since the real-world impact of COVID-19 on migraine patients has not been extensively studied, to the

best of knowledge.[19]

From the results of our study and other studies on COVID-19 pandemic's impact, it can be unanimously said that the pandemic has caused a negative effect on not only the impact on migraine/mental health of patients but also on the overall health status of the population.[20]

The study was not free from selection and observational bias and the fact that students of a single locality / presenting to a single hospital were included; a further multi-centered study with students from different background would be revealing more information regarding the increased frequencies of headache/migraine among students of online, e-learning.

CONCLUSION:

Increase in the use of digital devices amid the COVID-19 pandemic caused increased incidences of headache/migraine among the students. Additionally majority of students reported decrease in visual acuity during the pandemic due to which they had to wear glasses. Further studies are required for determining and addressing this health issue.

Authors Contribution:
Abdul Zahir: Manuscript Writing, Literature Review, Data Analysis and Research Monitoring

REFERENCES:

1. Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. Journal of Neuroscience. 2015;35(17):6619-29. https://doi.org/10.1523 /JNEUROSCI .0373-15.2015
2. Puledda F, Messina R, Goadsby PJ. An update on migraine: current understanding and future directions. Journal of neurology. 2017;264(9):2031-9. https://doi.org/10.1007 /s00415-017-8434-y
3. Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine progression: a systematic review. Headache: The Journal of Head and Face Pain. 2019;59(3):306-38. https://doi.org/ 10.1111/head.13459
4. Genizi J, Bugdnoskya V, Aboud A, Segal I, Assaf N, Srugo I, et al. Migraine and Tension-Type Headache Among Children and Adolescents: Application of International Headache Society Criteria in a Clinical Setting. Journal of Child Neurology. 2021 :0883073820988417. https://doi.org/10.1177 %2F0883073820988417
5. Leonardi M, Steiner TJ, Scher AT, Lipton RB. The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). The journal of headache and pain. 2005; 6(6):429-40. https://doi.org/10.1007/s10194-005-0252-4
6. Schwedt TJ. Preventive therapy of migraine. Continuum: Lifelong Learning in Neurology. 2018;24(4):1052-65. 10.1212/CON.0000000000000635
7. Stubberud A, Linde M. Digital technology and mobile health in behavioral migraine therapy: a narrative review. Current pain and headache reports. 2018;22(10):1-6. https://doi.org/ 10.1007 /s11916-018-0718-0
8. Eidlitz-Markus T, Zeharia A. Symptoms and clinical parameters of pediatric and adolescent migraine, by gender-a retrospective cohort study. The journal of headache and pain. 2017 :18(1):1-7. https://doi.org/10.1186/s10194-017-0789-z
9. Aboagye E, Yawson JA, Appiah KN. COVID-19 and E-learning: The challenges of students in tertiary institutions. Social Education Research. 2021:1-8. https://doi.org/10. 37256/ser.212021422
10. Radha R, Mahalakshmi K, Kumar VS, Saravanakumar AR. E-Learning during lockdown of Covid-19 pandemic: A global perspective. International journal of control and automation. 2020;13(4):1088-99.
11. Olesen J, Lipton RB. Migraine classification and diagnosis. International Headache Society criteria. Neurology. 1994;44(4):6-10.
12. Shantakumari N, Eldeeb R, Sreedharan J, Gopal K. Computer use and vision. related problems among university students in Ajman, United Arab Emirate. Annals of medical and health sciences research. 2014;4(2):258-63. https://doi.org/ 10.4103/ 2141-9248.129058
13. Birkie M, Endris M, Asnakew S. Determinants of migraine headache among regular undergraduate students, of Wollo University, Dessie, Ethiopia: cross–sectional study. BMC neurology. 2021;21(1):1-2. https://doi.org/10.1186/s12883-021-02466-4
14. Chowdhury D, Datta D. Managing migraine in the times of COVID-19 pandemic. Annals of Indian Academy of Neurology. 2020 Apr;23(1):33-9. https://dx.doi.org/ 10.4103 %2Faian.AIAN_296_20
15. Dutta S, Smita MK. The impact of COVID-19 pandemic on tertiary education in Bangladesh: students' perspectives. Open Journal of Social Sciences. 2020 ;8(09):53-68. http://www. scirp.org/journal/Paperabs.aspx?PaperID=102687
16. Silvestro M, Tessitore A, Tedeschi G, Russo A. Migraine in the time of COVID-19. Headache. 2020;60(5):988-9. https://dx. doi. org/10.1111%2Fhead.13803
17. Singh B, Gupta R, Garg R. Study of medical students and internet usage. International Journal of Scientific and Research Publications. 2013;3(5):1-5.
18. Majumdar P, Biswas A, Sahu S. COVID-19 pandemic and lockdown: cause of sleep disruption, depression, somatic pain, and increased screen exposure of office workers and students of India. Chronobiology international. 2020;37(8):1191-200. https://doi.org/10.1080/07420528.2020.1786107
19. Maatuk AM, Elberkawi EK, Aljawarneh S, Rashaideh H, Alharbi H. The COVID-19 pandemic and E-learning: challenges and opportunities from the perspective of students and instructors. Journal of Computing in Higher Education. 2021:1-8. https://doi.org/10.1007/s12528-021-09274-2
20. Tepecik Ýb, Kurt An, Hesapçioðlu St, Uðurlu M. Relationship between headache and Internet addiction in children. Turkish journal of medical sciences. 2019;49(5):1292-7. https://dx.doi.org/10.3906%2Fsag-1806-118

Original Article **Open Access**

COVID-19 Reporting and Data System (CO-RADS) for Assessment of Pulmonary Involvement and CT Severity Score in Predicting Disease Severity

Sadaf Tufail Butt, Muhammad Wasim Awan, Sana Farid, Hafsa Aziz, Wajiha Arshad, Mashkoor Ahmad

ABSTRACT

Objective: To assess diagnostic accuracy of HRCT for COVID pneumonia keeping RT-PCR as reference standard.

Study Design and Setting: A retrospective cohort study, carried out in of Radiology Department of KRL hospital, Islamabad from January 2021 to May 2021.

Methodology: A total of 199 patients referred to Radiology Department for HRCT examination with clinical suspicion of COVID pneumonia were enrolled. Average age was 54yrs ± 14. PCR results of patients were retrieved from MIS.

HRCT chest scan report assessed pulmonary involvement and categorized according to CORADS on a scale from 1 to 5. CT severity score was also assessed on 20-segment model for scoring. Statistical analysis was carried using SPSS software. Sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy were calculated.

Results: The sensitivity was calculated to be 99.05%, the specificity was36.84%, the positive predictive value was 86.25%, the negative predictive value was 90.63% and diagnostic accuracy was 88.61%"

For CORADS categories 1, 2 and 6, CT was in good agreement with the PCR results. Maximum numbers of patients were from age bracket 51-60 yrs. Correlation of gender with disease showed more prevalence in males and CTSS was not different in genders.

Conclusion: HRCT chest has high sensitivity and negative predictive value for diagnosis of COVID pneumonia on the basis of CORADS reporting scheme. However it has low specificity. Disease has more prevalence in male gender. The most severely affected age bracket was 51-60 years.

Key words: CORADS, COVID-19, CTSS, HRCT, RT-PCR

How to cite this Article:
Butt ST, Awan MW, Farid S, Aziz H, Arshad W, Ahmad M. COVID-19 Reporting and Data System (CO-RADS) for Assessment of Pulmonary Involvement and CT Severity Score in Predicting Disease Severity J Bahria Uni Med Dental Coll. 2022; 11(3):133-137 DOI: https://doi.org/10.51985/JBUMDC2021101

Sadaf Tufail Butt
Department of Radiology,
NORI and KRL Hospital, Islamabad
Email: drsadafpk@hotmail.com

Muhammad Wasim Awan
Head of Radiology Department
KRL Hospital, Islamabad
Email: drwasim71@gmail.com

Sana Farid
Resident, Department of Radiology
KRL Hospital, Islamabad
Email: sana-farid1@hotmail.com

Hafsa Aziz
PSO NORI, Department of Pathology,
NORI Hospital, Islamabad
Email: hafsa.aziz@gmail.com

Wajiha Arshad
Consultant, Department of Radiology
KRL Hospital
Email: drwajiha_rad@yahoo.com

Mashkoor Ahmad
Consultant, Department of Radiology
KRL Hospital
Email: mashahmad1@yahoo.com

Received: 10-Oct-2021
Accepted: 20-Jun-2022

INTRODUCTION:

SARS-Cov-2 causes an infection-related respiratory syndrome and was named Corona virus Disease 2019 by the World Health Organization.COVID-19 has evolved into a pandemic worldwide and declared emergency of international concern.[1] It was first detected in China in 2019 and soon spread over the globe. Despite the fact that china has finally kept the issue under control within the country only rare outbreaks and sporadic cases reported some parts of the country. However, the pandemic can last even longer as the virus is still spreading around the world.[2] Diagnosis of SARS-Cov-2 infection has prime importance to control the disease. Clinical picture may not be useful because the majority of patients are asymptomatic or have only mild symptoms.[3] Therefore for the diagnosis of SARS-Cov-2 infection sensitive and specific test were required. As a result real time PCR assay and antibody assay for the detection have been developed.[4]

According to the latest guideline of Diagnosis and Treatment protocol for COVID 19 (tentative 8th edition), the diagnosis of COVID-19 must be confirmed by means of (RT-PCR) or

gene sequencing of respiratory or blood specimens should be taken as a key indicator for hospitalization. However RT PCR has significantly low positive rate compared with HRCT due to limitations of sample collection, transportation and limitations in kit performance.[5]

According to the latest guideline of Diagnosis and Treatment protocol for COVID 19 (tentative 8th edition), the diagnosis of COVID-19 must be confirmed by means of (RT-PCR) or gene sequencing of respiratory or blood specimens should be taken as a key indicator for hospitalization.[6]

However RT PCR has significantly low positive rate compared with HRCT due to limitations of sample collection, transportation and limitations in kit performance.[5]

HRCT chest has proved to be of diagnostic value during current COVID 19 pandemic. It is fast, convenient, and effective method for early recognition of suspicious cases, hence aids in early quarantine. It carries high sensitivity for COVID -19 pneumonia, however it has lower specificity.[7]

The Dutch Radiological Society developed COVID-19 Reporting and Data System (CO-RADS) similar to the reporting systems TIRADS, LIRADS and BIRADS. It measures the possible pulmonary involvement by COVID-19 on scale from very low to very high (1to5). CO-RADS have proven to be a useful method for determining COVID-19 pulmonary involvement. It exhibits significant inter observer agreement in individuals with moderate to severe symptoms, particularly for categories 1 and 5.[8]

METHODOLOGY:

A single center retrospective cohort study conducted in Radiology department of KRL Hospital, Islamabad from January 2021 to May 2021on patients referred to radiology department for HRCT. The study included all the referred patients in the radiology department who were clinical suspicions of COVID pneumonia. Pregnant females due to the risk of CT, patients having pulmonary disease and malignancy were excluded. The research was approved by an independent ethical review board (KRL-HI-PUB-ERC/Oct21/08).

199 patients were recruited in this study to achieve 95% Level of the confidence interval and 5% margin error. Age range 20-92yrs (average age 54yrs ± 14). There were 77 females and 122 males.

These patients were tested by RT-PCR assays on material collected from throat with swab. The results of RT-PCR were obtained from hospital information system.

The RT-PCR results were extracted from the hospital information system.

HRCT chest scan of patients was done on 16-slicescanner; patients were scanned in supine position. History and clinical symptoms were recorded. A qualified radiologist reported the study. Each CT report assessed the pulmonary involvement and categorized according to CORADS on a scale from 1 to 5.

CORADS 1: normal or non-infectious, CORADS 2: typical for other infectious diseases rather than COVID 19, CORADS 3 : equivocal/uncertain features compatible with other diseases as well as COVID 19, CORADS 4 : high suspicious for COVID 19, CORADS 5: very high typical for COVID19), CORADS 6:(proven RTPCR positive for SARS-Cov-2.

CT severity score was also assessed and 20-segment model for scoring was followed and score was calculated out of total 40 points based on the percentage of lung parenchyma involved. Score of 19 out of 40 was considered as severe disease. Main CT features (ground-glass haze, crazy paving, consolidations, reticulation and/or thickened interlobular septa, nodules) were also described.

Patients were rejected when the time between RT-PCR test and the HRCT was more than seven days.

Statistical software (SPSS version 21) was used for analysis. Continuous variables are represented by means and standard deviation, while categorical variables are represented by counts and percentages.

RT-PCR assay was used as reference standard for COVID-19 infection.
CT –ve = CORADS 1 and 2
CT +ive = CORADS4, 5 and 6.
CT indeterminate/equivocal= CORADS 3

CT results in terms of CORADS were compared with PCR; the results were also studied in with respect to age and gender of patients The Pearson correlation coefficient test was used for correlations, and p-value less than 0.05 was defined statistically significant. The diagnostic accuracy sensitivity, specificity, positive predictive value (PPV) negative predictive value (NPV) were determined.

RESULTS:

All patients referred to KRL Radiology Department for HRCT were recruited in the study; their PCR reports were traced from database. A total of 199 patients were enrolled with age ranging 20-92 yrs (average age 54yrs ± 14) referred for HRCT examination with clinical suspicion of COVID pneumonia. There were 77 females and 122 males. Patients presented with cough, body aches, shortness of breath, fever and asymptomatic with history of contact, pre-surgical evaluation

Chi-square test was used to study the correlation between CT and PCR for diagnosis of COVID pneumonia. RT-PCR assay was used as reference standard for COVID-19 infection.

CORADS 1 and 2 considered CT negative for disease. CORADS 4, 5 and 6 CT positive for disease. CT indeterminate / equivocal= CORADS 3

Out of the PCR results, 105 patients turned out to be PCR positive and 94 were PCR negative. CT positive were 164, CT negative for disease were 35. The Sensitivity was

calculated as 99.05%, Specificity 36.84%, PPV 86.25%, NPV 90.63% and the diagnostic accuracy 88.61%. Table 1 shows sensitivity and specificity of CORADS.

For CORADS categories 1, 2 and 6,CT was in good agreement with the PCR results, and 99%patients were found PCR negative with p-value of <0.05. For CORADS category 3 which is indeterminate whether COVID pneumonia is present or not, all patients were PCR negative, p-value <0.001. For CORADS category 4, 50% patients were PCR negative although CORADS category states highly suspicious for COVID pneumonia. CORADS category 5 showed 71% were PCR negative and 28% were PCR positive and in agreement with the CT findings with significance value of <0.05.

Disease severity as assessed by (Chest CT scan Severity Score) CTSS according to age groups was also studied. Patients were divided in to groups according to their age: 20-30years old, >30-40years old, >40-50years old, >50-60yers old, >60-70years old, >70-80years old,.80-90years old, >90yeras old. Table3. Maximum number of patients were from age bracket 51-60 years followed by 61-70 years. Correlation of gender with disease showed more prevalence in males and CTSS was not different in genders with significance P value of <0.05. Table 4 shows correlation of gender with severity of disease based on CTSS.

Figure 1: HRCT chest lung window showing areas of ground glass haze with interlobular septal thickening, and intervening areas of increased attenuation, patient had CORADS category 5, CTSS 33/40, severe disease.

Figure 2: HRCT CHEST lung window showing patchy areas of ground glass haze with interlobular septal thickening in subpleural location, Patient was reported as CORADS category 5

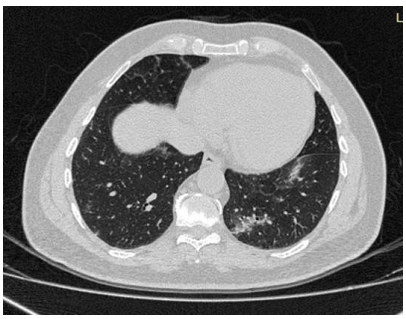


Table 1 Sensitivity and Specificity of the CORADS

CORADS	Gold Standard (PCR)		
	Positive	Negative	
Covid +ve	104	60	
Covid +ve	1	35	*P* <0.05
Total	105	95	
	Sensitivity 104/105*100=99.05%	Specificity 35/95*100=36.84%	

Table 2: Comparison of CT diagnosis based on CORADS vs PCR

CORADS	PCR +ve	PCR-ve	Total Patients
1	0	19	20
2	1	10	12
3	0	03	03
4	2	02	04
5	22	55	77
6	80	1	83

Table 3. Correlation of age groups with severity of the disease based on CTSS

Age Groups (Years)	CTSS (0-19) Mild	CTSS (20-40) Severe	Total No
20-30	12	0	12
>30-40	24	6	30
>40-50	24	5	29
>50-60	45	20	65
>60-70	27	11	38
>70-80	11	9	20
>80-90	3	0	3
>90	2	0	2

Table 4 .Correlation of gender of patients with severity of disease based on CTSS

Gender	CTSS (0-19) Mild	CTSS (20-40) Severe	Total No
Female	58	19	77
Male	90	32	122
	148	51	199

DISCUSSION:

COVID pneumonia has variable presentations. Patient may be an asymptomatic carrier. Due to its high infectivity it is important to isolate the infected person to further prevent spread of disease. This disease is susceptible to under diagnosis as well as misdiagnosis.[10] COVID-19 is diagnosed via detection of SARS-CoV-2 RNA using real time reverse-transcriptase polymerase chain reaction (RT-PCR), however as there is no gold standard investigation hence the performance of many SARS-CoV-2 RT-PCR assays is not entirely known. COVID 19 is diagnosed by real-time reverse transcriptase polymerase chain reaction to detect SARSCOV2 RNA .However the performance of various SARSCoV2 RT-

PCR assays is unknown due to the lack of gold standard research. Kanji et al. investigated the SARS-CoV-2 RT-false PCR's negative rate (FNR) and sensitivity, concluding that the assay's specificity is 100 percent and the false negative rate is affected by viral load changes over time.[11]

The study by Kanji et al evaluated the SARS-COV-2 RT PCR test sensitivity and false negative rate. It concludes that its specificity reaches 100% and the false negative rate of the assay is subject to viral load dynamics over time . False negative result is due to poor specimen collection, sampling at early stage of the disease process, low sensitivity of the assay, inappropriate sample type and low viral load[12-17]. We compared RT-PCR and HRCT chest for diagnosis of COVID pneumonia, keeping RT-PCR assay as reference standard for COVID-19 infection. The sensitivity was determined as 99%, the specificity was 58%, the positive predictive value was 54% the negative predictive value was 99% and the diagnostic accuracy was 72%. The study by Tao Ai[5] proposed that as RT-PCR has a low sensitivity, the false positive cases on CT can actually be the true positives as RT-PCR and found RT-PCR an imperfect gold standard test for the diagnosis of COVID-19. Our results were in agreement with the study conducted in Bangladesh by Haque S et al[18], they took RT-PCR as gold standard and calculated the diagnostic accuracy of HRCT. Their sensitivity was high about 96% in agreement with our study, specificity was low 66%, they had high PPV 97%, accuracy 90% and NPV 62%. Although it is not recommended to use CT chest for diagnosis of COVID 19 but it is shown to be helpful in assessment of complications, prognosis and severity. A study conducted by Korkmaz et al on the basis of their observations suggested that Chest CT can serve as a superior screening tool to RT-PCR in case of resource shortages in tests and "if patients with negative RT-PCR tests but positive CT findings are discharged without isolation or other precautionary measures, the rates of human-to-human transmission may increase, and the patients may deteriorate."[19] Our results were also in agreement with Mohammad Karam et al, they did meta-analysis of comparative studies assessing CT chest versus RT PCR, using RT-PCR as reference the sensitivity, specificity and accuracy was 0.91(0.82-0.98), 0.775 (0.25-1.00) and 0.87(0.68-0.99) respectively.[20] Efficacy of CT was assessed in terms of CORADS categories. For CORADS categories 1, 2 and 6, CT was in good agreement with the PCR results, and 99% patients were found PCR negative with P value of <0.05. For CORADS category 3 which is indeterminate whether COVID pneumonia is present or not, all patients were PCR negative, P value <0.05.As PCR had two categories, either the test has to be positive or negative, CT on the contrary reports in terms of probabilities, and for the purpose of calculation of sensitivity and specificity we considered CORADS 3 as disease negative. For CORADS category 4, 50% of the patients were PCR negative although CT based CORADS category states highly suspicious for COVID pneumonia.

CORADS category 5 showed 71% were PCR negative and 28% were PCR positive and in agreement with the CT findings with significance value of <0.05. A study by Prokop et al assessed diagnostic performance of CORADS and inter-observer agreement; they observed that CORADS permits the limits in terms of cut off points for clinical decision making. In addition it also provides good performance in anticipating COVID-19 patients with moderate to severe side effects. It have significant interobserver agreement, particularly for CO-RADS categories 1 and 5[8],however while assessing the diagnostic performance they found CORADS in good agreement with the reference standard (RT PCR), they also had a small group of patients who were both PCR and CT chest negative but clinical findings suggestive of COVID pneumonia.

In our study one of the reasons of low CT specificity might be the referral. As a part of medical department protocol, most of the patients referred for HRCT assessment were PCR negative and had strong clinical suspicion of COVID pneumonia, and those with PCR positive results were referred in less numbers. Only those PCR positive patients were referred to Radiology Department for HRCT who had some complications or had any comorbid. So there is probably sampling bias in our case. Still it shows high sensitivity and negative predictive value rendering it an effective tool for PCR negative cases with strong clinical suspicion.

Disease severity by CT Severity Score was also studied with respect to the age groups. We made groups of patients according to ages, groups were divided into 20-30yr, >30-40yr, >40-50yr, >50-60yr, >60-70yr, >70-80yr, 80-90yr and >90yr. Maximum number of patients were from age 51-70yrs, with highest CTSS in 51-60year age group. So either the younger age group is more resistant to infection or they get mild form of disease that does not reach hospital to get investigated. Our results were in agreement with the Saeed et al; they found severe disease mainly in 50-59 year age group, although they did 25 point scoring system and classified the disease severity into mild, moderate and severe on the basis of CTSS where as we classified it into two categories, mild and severewith 40 point scoring system.[21] Another study done by Zayed, et al[22] reported that both CTSS and CORADS scores performed well in predicting COVID-19 they also observed severe illness in the older age groups

Association of gender with disease was also studied, it was found to be more prevalent in males, however the disease severity as assessed by CTSS was not different between genders. Saeed et al also found male predominance in disease.[21] Our results were in disagreement with the study by E forsblom et al, they found that both sexes were equally infected by SARS-CoV2, although this study was population based registry, it was not imaging based study; it was rather

based of clinical and pathological parameters.[23] They also found more severe disease in males as compared to female population. In our study one of the reasons of low CT specificity might be the referral which is one of the limitations of the study. As most of the patients referred for HRCT assessment were PCR negative and had strong clinical suspicion of COVID pneumonia, while those with PCR positive results were referred in less numbers. Only those PCR positive patients were referred to Radiology Department for HRCT who had some complications or had any comorbid. So there is probably sampling bias.

CONCLUSION:

HRCT chest has high sensitivity and negative predictive value for diagnosis of COVID pneumonia on the basis of CORADS reporting scheme. However, it has low specificity when RT PCR is taken as reference standard. Disease has more prevalence in male gender, however the disease severity as assessed by CTSS was not different between genders with the most severely affected age bracket 51-60yrs.

Authors Contribution:
Sadaf Tufail Butt: Conception, design, analysis and interpretation of data, drafting paper
Muhammad Waseem Awan: Concept, design
Sana Farid: Design and Data Collection
Hafsa Aziz: Data analysis
Wajiha Arshad: Interpretation of data
Mashkoor Ahmad: Interpretation of data

REFERENCES

1. Tang JW, Tambyah PA, Hui DS. Emergence of a novel coronavirus causing respiratory illness from Wuhan, China. Journal of infection. 2020;80(3):350-71. DOI: 10.1016/j.jinf.2020.01.014
2. Gui-Qiang W, Lei Z, Xia W, Yan-Mei J, Fu-Sheng W. Diagnosis and Treatment Protocol for COVID-19 Patients (Tentative 8th Edition): Interpretation of Updated Key Points. Infectious Diseases & Immunity. 2021;1(01):17-9. doi.org/10.1097/ID9.0000000000000002
3. Kovács A, Palásti P, Veréb D, Bozsik B, Palkó A, Kincses ZT. The sensitivity and specificity of chest CT in the diagnosis of COVID-19. European Radiology. 2021;31(5):2819-24. DOI: 10.1007/s00330-020-07347-x
4. Aziz H, Fatima S, Mahmood H, Muhammad S, Saeed MA, Khurshid S, et al. Antibody Response to SARS-CoV-2 in Relation to the Contributing Factors in COVID-19 Patients. Viral Immunology. 2022. DOI: 10.1089/vim.2021.0097
5. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020;296(2):E32-E40. doi: 10.1148/radiol.2020200642
6. Aziz H, Fatima S, Iqbal H, Faheem M. Recent advances in molecular diagnosis curbing the COVID-19. International Journal of Infectious Diseases. 2020;97:322-5. DOI: 10.1016/j.ijid.2020.06.004
7. Xu B, Xing Y, Peng J, Zheng Z, Tang W, Sun Y, et al. Chest CT for detecting COVID-19: a systematic review and meta-analysis of diagnostic accuracy. European radiology. 2020;30(10):5720-7. DOI: 10.1007/s00330-020-06934-2
8. Prokop M, Van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, et al. CO-RADS: a categorical CT assessment scheme for patients suspected of having COVID-19—definition and evaluation. Radiology. 2020;296(2):E97-E104. DOI: 10.1148/radiol.2020201473
9. Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, et al. Chest CT severity score: an imaging tool for assessing severe COVID-19. Radiology: Cardiothoracic Imaging. 2020;2(2):e200047. DOI: 10.1148/ryct.2020200047
10. Waller JV, Kaur P, Tucker A, Lin KK, Diaz MJ, Henry TS, et al. Diagnostic tools for coronavirus disease (COVID-19): comparing CT and RT-PCR viral nucleic acid testing. American Journal of Roentgenology. 2020;215(4):834-8. DOI: 10.2214/AJR.20.23418
11. Kanji JN, Zelyas N, MacDonald C, Pabbaraju K, Khan MN, Prasad A, et al. False negative rate of COVID-19 PCR testing: a discordant testing analysis. Virology journal. 2021;18(1):1-6. DOI: 10.1186/s12985-021-01489-0
12. Kinloch NN, Ritchie G, Brumme CJ, Dong W, Dong W, Lawson T, et al. Suboptimal biological sampling as a probable cause of false-negative COVID-19 diagnostic test results. The Journal of infectious diseases. 2020;222(6):899-902. DOI: 10.1093/infdis/jiaa370
13. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction–based SARS-CoV-2 tests by time since exposure. Annals of internal medicine. 2020;173(4):262-7. DOI: 10.7326/M20-1495
14. Prinzi A. False negatives and reinfections: the challenges of SARS-CoV-2 RT-PCR testing. American Society for Microbiology, april. 2020;27:2020.
15. Yang Y, Yang M, Shen C, Wang F, Yuan J, Li J, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. MedRxiv. 2020. doi: 10.1016/j.xinn.2020.100061
16. Pan Y, Long L, Zhang D, Yuan T, Cui S, Yang P, et al. Potential false-negative nucleic acid testing results for severe acute respiratory syndrome coronavirus 2 from thermal inactivation of samples with low viral loads. Clinical chemistry. 2020;66(6):794-801. DOI: 10.1093/clinchem/hvaa091
17. He X, Lau EH, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nature medicine. 2020;26(5):672-5. DOI: 10.1038/s41591-020-0869-5
18. Haque S, Chowdhury N, Nabi S, Ara H, Mahfuza M, Shamsunnahar S, et al. Role of HRCT Imaging in Diagnosis And Prognosis of Novel Corona (Covid-19) Pneumonia, Radiologists Experience in Dhaka Medical College Hospital Correlated with Rt-PCR. Journal of Dhaka Medical College. 2020;29(2):110-5. doi.org/10.3329/jdmc.v29i2.51184
19. Korkmaz I, Dikmen N, Keleº FO, Bal T. Chest CT in COVID-19 pneumonia: correlations of imaging findings in clinically suspected but repeatedly RT-PCR test-negative patients. Egyptian Journal of Radiology and Nuclear Medicine. 2021;52(1):1-9. doi.org/10.1186/s43055-021-00481-6
20. Karam M, Althuwaikh S, Alazemi M, Abul A, Hayre A, Alsaif A, et al. Chest CT versus RT-PCR for the Detection of COVID-19: Systematic Review and Meta-analysis of Comparative Studies. MedRxiv. 2020. DOI: 10.1177/20542704211011837
21. Saeed GA, Gaba W, Shah A, Al Helali AA, Raidullah E, Al Ali AB, et al. Correlation between chest CT severity scores and the clinical parameters of adult patients with COVID-19 pneumonia. Radiology Research and Practice. 2021;2021. DOI: 10.1155/2021/6697677
22. Zayed NE, Bessar MA, Lutfy S. CO-RADS versus CT-SS scores in predicting severe COVID-19 patients: retrospective comparative study. The Egyptian Journal of Bronchology. 2021;15(1):1-10. doi.org/10.1186/s43168-021-00060-3

Original Article **Open Access**

Effect of Smoking on Peridontal Health: A Comparative Study

Faisal Salim, Chander Kumar, Seeme Nigar, Sabeen Masood, Muhammad Asif Raz, Bilal Sarwar

ABSTRACT

Objective: To determine the association between smoking and calculus deposition among patients presenting at a tertiary hospital of Karachi.

Study Design and Settings: A cross-sectional comparative study was conducted at periodontology OPD, Altamash Institute of Dental Medicin,e Karachi for six months from 15- September-2021 to 15-February-2022.

Methodology: About 150 male patients of age 11 to 60 years coming for routine check-ups were included. Patients were divided into two groups on basis of their smoking status. Clinical examination was performed for each tooth and presence of calculus was evaluated using Oral Hygiene Index (OHI).The measurement of calculus was done by visual investigation and tactile examination by using periodontal probe and mirror. For each individual, one tooth was selected from each sextant and average OHI score is calculated. Supra-gingival calculus present near marginal gingiva was labeled as mild whereas supra and sub gingival calculus with gum recession along with calculus covering more than half of tooth surface was labeled as severe.

Results: Among 75 smokers, 44% had mild and 56% had severe calculus deposition whereas among 75 non-smokers, 86.7% had mild and 13.3% had severe calculus deposition. Odds of smoking among patients with severe deposition is 8.27 times higher than odds of smoking among patients with mild calculus deposition (OR=8.27, 95% CI=3.69-18.53) and significant effect of smoking was observed on calculus deposition (p=0.001).

Conclusion: The study concluded that smoking has significant effect on calculus deposition. By taking smoking as a discriminant variable it is proved that calculus deposition is higher in smokers as compared to non-smokers.

Keywords: Smoking, periodontal health, calculus deposition, oral hygiene

How to cite this Article:

Salim F, Kumar C, Nigar S, Masood S, Raz MA, Sarwar B. Effect of Smoking on Peridontal Health: A Comparative Study. J Bahria Uni Med Dental Coll. 2022; 11(3):138-142 DOI: https://doi.org/10.51985/JBUMDC2021102

Faisal Salim
Senior Dental Surgeon, Department of Periodontology
Benai Bhutto Hospital Quetta
Email: faisal_salim28@yahoo.com

Chander Kumar
Associate Professor, Department of Periodontology
Dow University Health Sciences
Email: chander.kumar@duhs.edu.pk

Seeme Nigar
Registrar, Department of Oral Pathology
Altamash Institute of Dental Medicine, Karachi
Email: dr.seeme.nigar@gmail.com

Sabeen Masood
FCPS Resident, Department of Operative Dentistry and Endodontics
Altamash Institute of Dental Medicine, Karachi
Email: sabeen_786@live.com

Muhammad Asif Raz
Assistant Professor, Department of Management Sciences
Baluchistan University of Information Technology, Engineering and Management Sciences, Quetta
Email: asif.raz@buitms.edu.pk

Bilal Sarwar
Assistant Professor, Department of Management Sciences
Baluchistan University of Information Technology, Engineering and Management Sciences, Quetta
Email: bilal.sarwar@buitms.edu.pk

Received: 10-Oct-2021
Accepted: 28-Jun-2022

INTRODUCTION

Periodontal disease (PD) is an infectious, chronic condition accompanied by the loss of periodontal tissue and affecting almost 20-50% of global population. It is generally accepted that PD occurs as a consequence of imbalances between local microbiota and locally mediated immune response. Chronic PD displays a gender, age, and socio-economic status differences, indicating that socio-demographic-related variables have played a significant role in the disease growth accounting for around 8% increase in prevalence rate of periodontitis in an age- standardized population from 1990 to 2019.[3] One of the modifiable and unhealthy lifestyle risk factors of PD is smoking. Smoking plays a significant part in the development and progression of chronic PD.[4,5,6,7] Worldwide, mortality rates as a consequence of smoking are estimated to be 7 million in a year.[8] Worldwide, about 43% of the women and 57% of the men are smokers. In developing countries, the smoking rate is increasing by 3% each year, which may also leads to increase in prevalence of PD.[6] In terms of the process by which smoking influences the development of periodontitis, multiple causes lead to the harmful periodontal impacts of smoking, comprising the modification of both host reaction and microbial mechanisms. Even healthy periodontium is damaged by smoking and

certain complications for example diabetes mellitus multiplies the destructive effect involved in smokers. [10] In another study increased incidence of calculus has been indicated in Community Periodontal Index (CPI) scores in smokers. [11] Among the environmental factors, tobacco smoking is considered one of the true risk factors and is known to be independently related to periodontal destruction. More than seven thousand toxins are present in tobacco smoke including, carcinogens and addictive psycho-active substances like nicotine, which are detrimental to general health and also a major public health concern. In addition, the use of smokeless tobacco (SLT) as an alternative tobacco product to cigarette smoking is gradually becoming popular.

Considering the well-established deleterious effects of smoking on periodontal health, it is of great importance to understand the underlying mechanisms, which remain largely unclear. Its widely accepted that both periodontal microflora and host response play critical roles in the initiation and progression of periodontal disease. Considerable attention has been focused on the effects of smoking on host response in previous studies, which demonstrate that smoking increases the host's susceptibility and risk of infection by inducing immune dysfunction. However, it is still necessary to carry out a more detailed assessment of the effects of smoking on sub-gingival microflora that causes the infectious disease. A previous review article investigated the correlation between smoking and oral and nasopharyngeal bacterial flora, and demonstrated the adverse effects of smoking on the colonization of potential pathogens and the increased frequency of upper respiratory tract infections.[1]

The aim of current study was to determine the association between smoking and calculus deposition among patients presenting at a tertiary hospital of Karachi. This study would help in promoting healthy practices and increasing awareness regarding harmful effects of smoking in general and associated with calculus decomposition.

METHODOLOGY:

A cross-sectional comparative study was conducted at the out-patient department of periodontology of Altamash Institute of Dental Medicine, Karachi for the duration of six months from 15-September 2021 to 15-February 2022, after the approval of institutional review board with ERC code: AIDM/ERC/20/2021/01. Sample size was estimated using online Open epi sample size estimator, by statistics of mean calculus index in smokers as 1.62 ± 0.36 and in non-smokers as 1.40 ± 0.55, power of test as 80% and 95% confidence interval.[12] The estimated sample size came out as 71˜75 in each group, total sample size was 150. All the male patients of age 11 to 60 years coming for routine check-ups were included in the study using non-probability convenience sampling technique. Patients who were consuming smokeless tobacco or who had systemic illness were excluded from the study. The informed consent was taken from all the eligible participants before starting data collection. Baseline information was collected from all the patients and noted on simple pre-designed proforma. Patients were divided into two groups on the basis of their smoking status. "Group A" included 75 patients who had previous history of smoking or who were currently smokers. "Group B" included 75 patients who had never smoked in their whole life.

The clinical examination was performed for each tooth and presence of calculus was evaluated using Oral Hygiene Index (OHI) by principal investigator. The measurement of calculus was done by visual investigation and tactile examination by using periodontal probe and mirror. For each individual, one tooth was selected from each sextant and the average OHI score is calculated. Supra-gingival calculus present near marginal gingiva was labeled as mild whereas supra and sub gingival calculus with gum recession along with calculus covering more than half of tooth surface was labeled as severe. The level of calculus deposition was recorded for both groups i.e., smokers and non-smokers.

Data was analyzed using SPSS version 23. Mean and SD were calculated for numeric variables and frequency and percentage were reported for categorical variables. Comparison between both groups for calculus deposition was done using chi-square test. P<=0.05 was taken as statistically significant.

RESULTS

Out of 150 patients, most of the patients were of age 41-60 years (44.7%), followed by 21-40 years (39.3%) and 11-20 years (16%) respectively. About 52 had education till intermediate (34.7%), 43 had bachelors or master's degree (28.7%), 38 did matric (25.3%), 13 had primary level education (8.7%) and only 4 were illiterate (2.7%). Most of the patients brush their teeth once a day (52.7%) and 27.3% patients brush their two times in a day. About 48.7% of the patients floss their teeth occasionally and 22.7% had never used floss . However, we did not find any statistically significant correlation between both brushing habits among smokers and flossing habit among smokers (p>0.05). Most of the smokers who had severe calculus in their mouths complained of frequent bleeding from gingiva (n=25) and bleeding while brushing (n=12). We found their relation to be statistically significant (p=0.001) (Fig 3). Out of 150 patients, 35% had severe calculus deposition and 65% had mild calculus deposition. Among 75 smokers, 44% had mild and 56% had severe calculus deposition whereas among 75 non-smokers, 86.7% had mild and 13.3% had severe calculus deposition. Hence, the odds of smoking among patients with severe deposition is 8.27 times higher than odds of smoking among patients with mild calculus deposition (OR=3.5, 95% CI=2.01-6.15). Hence, the significant effect of smoking was observed on calculus deposition (p=0.001). (Fig 1)

For age group 11-20 years, patients who were smokers had low frequency of severe calculus deposition. In this age

group, statistically insignificant difference was observed between smoking and calculus deposition (p=0.473). For age group 21-40 years, low frequency of severe calculus deposition was observed among smokers, whereas in age group 41-60 years, high frequency of severe calculus was observed among smokers. In these age groups, statistically statistically significant difference was observed between smoking and calculus deposition (p<0.05). (Table 1)

Figure 1: Relation of Gingival Bleeding in Smokers and Non-smokers against calculus condition

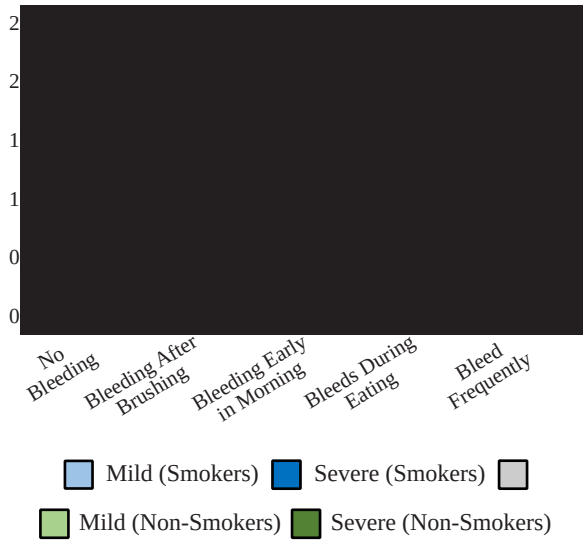


Figure 2: Age wise incidence of calculus deposition among smokes

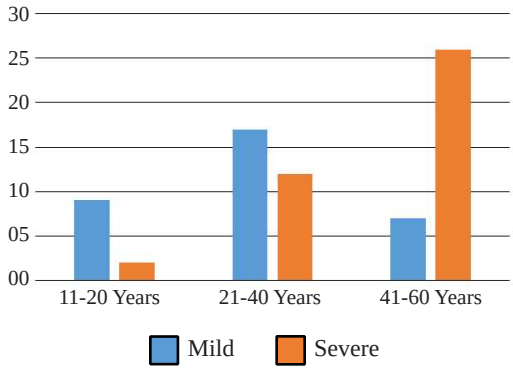


Table 1: Significant effect of smoking on calculus deposition with respect to age

Age groups	Smoking	Mild	Severe	Total		P-value
11-20 years	Yes	9 (81.8%)	2 (18.2%)	11	24	0.437
	No	12 (92.3%)	1 (7.7%)	13		
21-40 years	Yes	17 (56.7%)	13 (43.3%)	30	59	0.02
	No	25 (86.2%)	4 (13.8%)	29		
41-60 years	Yes	7 (20.6%)	27 (79.4%)	34	67	0.001
	No	28 (84.8%)	5 (15.2%)	33		
Total		98	52			

DISCUSSION

Smoking has become a significant public health issue due to its associated morbidity and fatality which is attributed to raise from 7 million per year to 8.3 million by 2030.[8] This research was conducted to determine the significant effect of smoking on calculus deposition. We have included only males (100%) in our study, the females were excluded because it was difficult to enroll them and make them admit that they practice cigarette smoking. Another reason of not including females was to avoid potential bias in results due to hormone-induced microcirculatory alterations to the periodontal health condition.[13,14] According to the results presented in the research paper by Ho K Y et al. most of the participants they studied (68.7%) started smoking in as early as 13 to 18 years of their age.[15] However contrary to this, in the present study, only 32.9% of the participants who smoked were of age less than 30 years which might be because of the small sample of the population while high proportion of smokers were found in age greater than 30 years (67.1%). According to the studies by et al. and A.N. Haas et al. higher deposition of calculus is often associated with habit of smoking.[16,17,18] because smoking reduces the speed of response of host defenses rendering the healing ability impaired and promoting the calculus formation via reduced salivary flow and vasoconstriction in gingival capillaries.[19] Findings in this study indicate association of calculus presence in mouths of smokers, with ages ranging from 21 to 40 years and 41 to 60 years with statistical significance of p=0.036 and p=0.001 respectively; it is also in concordance with the aforementioned studies.[15-18] Age can be a confounding factor in increasing the severity of calculus deposition especially among smokers.[20]

Woelber et al. and demonstrated no difference in oral hygiene of smokers vs non-smokers via oral hygiene-related self-efficacy (OHSE) scale.[21, 22] However, smoking is a risk factor for poor periodontal disease and this study revealed the poor oral hygiene among smokers in terms of more participants complaining of frequent bleeding and bleeding after brushing.[22]

Moreover, flossing has a positive impact on reducing gingival inflammation and level of plaque. The induction of chemical mineralization inhibitors in toothpastes or mouthwashes help to stop the formation of calculus forming agents by delaying the calcification of plaque which keep the deposits in an amorphous non hardened state so it can be removed with the help of brushing and flossing. It has been found that oral hygiene improving habits were influenced by the habit of smoking. Non-smokers were more conscious about the condition of their hygiene, non-smokers were more frequently brushing their teeth and were more consistent in visiting their dentists for maintaining good oral hygiene. Twice a day brushing and once per day flossing is the recommendation of The American Dental

Association (ADA) in removing the microbial plaque and to prevent gingivitis.

In the present study, age factor and less education were associated with severe calculus deposition. Aging has been studied in depth in periodontal epidemiology and has been demonstrated to be associated with poorer oral hygiene habits, which could account for age related effects.[23] Elderly individuals who need help with brushing have higher level of calculus. In addition, it has been reported that periodontal disease often occurs in elderly individuals with poor health activities and conditions .[24]

Several limitations should be considered in the results of this study. As this study is conducted in a small population with convenience sampling with a defined age range, information can be more readily gathered in a general health study and reinforce including oral health parameters in such studies. As a result of limited availability of resources (time constraints, hesitance of some people to participate in the survey) these findings may not be representative of the entire population of Karachi. Other possible confounders such as attitude, lifestyle, stress and socio-economic status are not included in this study.

The findings of this research offer a forum for potential studies that can aid in improving oral health and hygiene. The findings of the research would be useful for both the general public and health decision leaders in creating community education campaigns regarding the impact of smoking on overall health as well as oral health. One of the limitation, current study was small size, which makes it difficult to infer the results on target population.

CONCLUSION:

The current study concluded that smoking has significant effect on calculus deposition. Dental examination is an important way in reducing calculus deposition as continuous visits improve the oral hygiene and guide the individual of treatment possibilities and to make on time decisions which ultimately reduces the amount of calculus deposition. Based on the results we can conclude that by taking smoking as a discriminant variable it is proved that calculus deposition is higher in smokers as compared to non-smokers.

Authors Contribution:
Faisal Salim: Topic selection, Data collection, Statistical Analysis, Article Writing
Chander Kumar: Supervisor, Proof reading
Semme Nigar: Data Collection, Article Writing
Sabeen Masood: Data Collection, Article Writing
Muhammad Asif Raz: Article writing, collection of references
Bilal Sarwar: Article writing, collection of references

REFERENCES

1. Nazir MA. Prevalence of periodontal disease, its association with systemic diseases and prevention. Int J Health Sci (Qassim). 2017;11(2):72-80. PMID: 28539867; PMCID: PMC5426403.
2. Usui M, Onizuka S, Sato T, Kokabu S, Ariyoshi W, Nakashima K. Mechanism of alveolar bone destruction in periodontitis—Periodontal bacteria and inflammation. Jpn Dent Sci Rev. 2021; 57:201-8.
3. Chen MX, Zhong YJ, Dong QQ, Wong HM, Wen YF. Global, regional, and national burden of severe periodontitis, 1990–2019: An analysis of the Global Burden of Disease Study 2019. J. Clin. Periodontol. 2021;48(9):1165-88.
4. Gautam DK, Jindal V, Gupta SC, Tuli A, Kotwal B, Thakur R. Effect of cigarette smoking on the periodontal health status: A comparative, cross sectional study. J Indian Soc Periodontol. 2011;15(4): 383-7.DOI: 10.4103/0972-124x.92575.
5. Griffin SO, Jones JA, Brunson D, Griffin PM, Bailey WD. Burden of oral disease among older adults and implications for public health priorities. Am J Public Health. 2012;102(3): 411-8. DOI: 10.2105/ajph.2011.300362.
6. Baumeister SE, Freuer D, Nolde M, Kocher T, Baurecht H, Khazaei Y, Ehmke B, Holtfreter B. Testing the association between tobacco smoking, alcohol consumption, and risk of periodontitis: A Mendelian randomization study. Journal of Clinical Periodontology. 2021;48(11):1414-20.
7. Leite FR, Nascimento GG, Scheutz F, Lopez R. Effect of smoking on periodontitis: a systematic review and meta-regression. American journal of preventive medicine. 2018; 54(6):831-41.
8. Yang JJ, Yu D, Wen W, Shu XO, Saito E, Rahman S, Gupta PC, He J, Tsugane S, Xiang YB, Gao YT. Tobacco smoking and mortality in Asia: a pooled meta-analysis. JAMA network open. 2019;2(3):e191474-.
9. Balto HA, Alabdulaaly L, Bahammam S, Asma'a A. Comparative analysis of prevalence of apical periodontitis in smokers and non-smokers using cone-beam computed tomography. The Saudi dental journal. 2019;31(1):52-7.
10. Battancs E, Gheorghita D, Nyiraty S, Lengyel C, Eördegh G, Baráth Z, Várkonyi T, Antal M. Periodontal disease in diabetes mellitus: A case–control study in smokers and non-smokers. Diabetes Therapy. 2020;11(11):2715-28.
11. Gill PS. Assessment of prevalence of periodontitis among smokers and non-smokers: A comparative study. J Adv Med Dent Scie Res 2019;7(12): 149-152.
12. Sreedevi M, Ramesh A, Dwarakanath C. Periodontal status in smokers and nonsmokers: a clinical, microbiological, and histopathological study. Int J Dent.;2012: 571590.DOI: 10.1155 /2012/571590.
13. Agrawal R, Ahmed H, Soorgani N, Naik L, Reddy S, Medabalmi M. Assessment of Periodontal Status in Pre- and Postmenopausal Women with Chronic Periodontitis: A Cross-Sectional Study. *J Pharm Bioallied Sci*. 2021;13(Suppl 2): S997-S999. doi: 10.4103/jpbs.jpbs_145_21.
14. Jafri Z, Bhardwaj A, Sawai M, Sultan N. Influence of female sex hormones on periodontium: A case series. Journal of natural science, biology, and medicine. 2015;6(Suppl 1): S146.

15. Ho KY, Li HC, Lam KK, Chan SS, Wang MP, Chan VW, Xia VW, Lam TH. Exploratory study on the relationship between smoking and other risk behaviours among young smokers. Journal of Clinical Nursing. 2018;27(13-14):2859-67.

16. Oppermann RV, Haas AN, Rösing CK, Susin C. Epidemiology of periodontal diseases in adults from Latin America. Periodontology 2000. 2015;67(1):13-33.

17. Haas AN, Prado R, Rios FS, Costa RD, Angst PD, Moura MD, Maltz M, Jardim JJ. Occurrence and predictors of gingivitis and supragingival calculus in a population of Brazilian adults. Brazilian oral research. 2019;33.

18. Hussain M, Riasat M, Nisa WU, Ullah F, Shaid F. Assessment of effect of Cigarette Smoking on Periodontal Health of Patients Reporting to Dental Section of Bacha Khan Medical College Mardan. Pakistan Journal of Public Health. 2020;10(3):185-9.

19. Boi-Ukeme CO, Azodo CC. Relating oral hygiene, gingival, and periodontal status with nicotine dependence among smokers-A cross-sectional study. Journal of Clinical Sciences. 2020;17(4):127.

20. Robbihi HI, Sulaeman ES, Rahardjo SS. Path analysis: the effect of smoking on the risk of periodontal disease. Indonesian Journal of Medicine. 2018;3(2):99-109.

21. Woelber JP, Bienas H, Fabry G, Silbernagel W, Giesler M, Tennert C et al. Oral hygiene-related self-efficacy as a predictor of oral hygiene behaviour: a prospective cohort study. J Clin Periodontol. 2015; 42:142-149.

22. Sarsilmazer G, Atilla G. The relationship between oral hygiene-related self-efficacy, general self-efficacy and daily plaque control. International Journal of Dental Hygiene. 2020;18(2) :182-91.

23. Bidinotto AB, Martins AB, Dos Santos CM, Hugo FN, Hilgert JB, Celeste RK, Padilha DM, De Marchi RJ. Four-year incidence rate and predictors of root caries among community-dwelling south Brazilian older adults. Community Dent Oral Epidemiol. 2018;46(2):125-131. Doi: 10.1111/cdoe.12343. Epub 2017 Sep 18. PMID: 28921685.

24. Zellmer M, Gahnberg L, Ramberg P. Prevalence of halitosis in elderly living in nursing homes. Int J Dent Hyg. 2016 ;14(4): 295-300.Doi: 10.1111/idh.12236. Epub 2016 Aug 1. PMID: 27476817.

Original Article **Open Access**

Echocardiography Based Assessment of Cardiac Function in Patients With Reno-cardiac Syndrome

Nadia Shams, Muhammad Hussain Baloch, Furquana Niaz, Lubna Meraj, Mubarak Ali

ABSTRACT

Objectives: There is rising world-wide burden of chronic kidney disease (CKD) with high Cardio-vascular mortality. This research aims to study echocardiography based cardiac function with respect to CKD stages.

Study Design and Setting: This cross-sectional study was conducted at RIHS Islamabad (Jan 2021–Jan 2022) after ethical approval.

Methodology: Total 130 adult CKD cases were included by consecutive sampling. Acute kidney injury and diagnosed/treated cases of cardiac disease were excluded. BMI and GFR was calculated. CKD staging done by KDOQI-classification. Cardiac impairment categorized by ECG and Echocardiography. Data analyzed by SPSS V-22 with Chi-square test.

Results: Amongst 130 CKD cases, there were 66(51%) males and 64(49%) females. Mean age was 60+13.27 years, mean BMI was 24+4.2. Diabetes mellitus was observed in 100(76.9%), hypertension in 122(93.8%). Mean creatinine was 4.83mg/dl and mean GFR was 17.84 mL/min/1.73m^2. Twenty-five(19.2%) patients were on hemodialysis. Mean cardiac EF was 49.18%**.** EF was normal in 39(30%), mildly reduced in 40(30.8%), moderately reduced in 29(22.3%) and severely reduced in 22(16.9%), diastolic dysfunction seen in 08(6.2%). Twenty-five(18.5%) cases had congestive cardiac failure; 14(56%) compensated and 11(44%) decompensated CCF. There was significant association between GFR and EF ($p<0.0001$).

Conclusions: Decline in cardiac function is associated with advanced CKD stages. Cardiac evaluation suggested at initial presentation of CKD, hence diagnosing asymptomatic compensated heart failure. Study finds high burden of diabetes, hypertension, anemia and IHD in CKD cases. GFR should be used rather than isolated creatinine in CKD. High clinical suspicion and early intervention may lead to better outcome.

Key Words: Chronic Kidney disease, Estimated Glomerular filtration rate, Reno-cardiac Syndrome, KDOQI classification.

How to cite this Article:
Shams N, Baloch MH, Niaz F, Meraj L, Ali M. Echocardiography Based Assessment of Cardiac Function in Patients With Reno-cardiac Syndrome. J Bahria Uni Med Dental Coll. 2022; 11(3):143-147 DOI: https://doi.org/ 10.51985 /JBUMDC202243

INTRODUCTION:

Chronic Kidney Disease (CKD) is presence of structural and functional kidney damage for >3 months, irrespective of cause.[1] Patients with CKD frequently experience cardiovascular and other co-morbidities.[2] Global burden of CKD is on rise with estimated prevalence 8-16%.[3] A community-based study conducted in Karachi in 2014 reported CKD prevalence of 12.5%.[4] However, higher prevalence of 29.9% observed in a south-Asian study by Jafar et al.[5]

CKD is an inflammatory state with various implications, especially on microvasculature.[6] Cardio-renal axis plays role in maintaining effective extracellular circulating volume. Equilibrium is maintained by various mechanisms i.e., volume/pressure sensors, neurohormonal feedback loops, vasoactive substances, transporters, rennin-angiotensin-aldosterone system, endothelin's, arginine, vasopressin & natriuretic peptides.

Reno-cardiac syndrome (RCS) is defined as CKD leading to progressive secondary cardiac dysfunction. including structural abnormalities like fibrosis, left ventricular (LV) hypertrophy or functional changes like ischemia, arrhythmia and systolic/diastolic dysfunction. There is no single diagnostic biomarker or imaging modality for RCS. Hence, the most common inclusion criterion is underlying CKD or

Nadia Shams
Professor Department of Medicine
Rawal Institute of Health Science, Islamabad
Email: nadia_shams@yahoo.com

Muhammad Hussain Baloch
Associate Professor, Department of Nephrology
Rawal Institute of Health Science, Islamabad
Email: dr.hussainbaloch@gmail.com

Furquana Niaz
Professor, Department of Dermatology
Karachi Institute of Medical Sciences, Karachi
Email: furquananiaz@hotmail.com

Lubna Meraj
Associate Professor, Department of Medicine
Benazir Bhutto Hospital - Rawalpindi Medical University
Email: lubnamerajch@gmail.com

Mubarak Ali
Registrar, Post Graduate Trainee, Department of Medicine
Rawal Institute of Health Science Islamabad
Email: Mubarak1214@yahoo.com

Received: 24-Mar-2022
Accepted: 17-May-2022

ESRD with coexisting cardiac pathology.[7,8]

Leading cause of mortality and morbidity across spectrum of CKD is overwhelming cardiovascular disease having higher risk association with microalbuminuria or reduced GFR. Cardiovascular disease in CKD manifest in variety of ways like atherosclerosis, arteriosclerosis, LV hypertrophy, reduced LV contractility, impaired LV relaxation, pericardial effusion, aortic & mitral valve disease, mitral annular calcification, endocarditis, atrial fibrillation and ventricular arrhythmias that may lead to sudden cardiac death. There is higher incidence of both ischemic and hemorrhagic events than general population. Not surprisingly, cardiovascular disease is also associated with cerebro-vascular manifestations in CKD cases, including cognitive decline.

Approximately 50% mortality in end stage renal disease (ESRD) is attributed to cardiovascular events, including myocardial infarction, sudden cardiac death, arrythmias and cardiomyopathy.[9] The electrolyte imbalances, in particular hyperkalemia, associated co-morbidities i.e., diabetes, hypertension and dyslipidemia also attribute to cardiovascular morbidity and mortality in CKD.

Data from this study will highlight importance of cardiac evaluation in CKD cases. Hence, timely screening and intervention for reno-cardiac syndrome may reduce the mortality and morbidity. This may guide us regarding protocols of cardiac evaluation in CKD and identifying high cardiovascular risk cases that need to be evaluated and intervened.

METHODOLOGY:

This cross-sectional study was conducted at Dept. of Medicine and Nephrology at Rawal Institute of Health Sciences Islamabad from 1st January 2021 to 1st January 2022. Research was conducted after ethical approval by research and ethics committee of RIHS (ERC# RIHS-REC/056/20).

The 130 diagnosed adult CKD patients (age>18 years) of both the genders were included. Acute kidney injury, previously diagnosed or treated cases of cardiac impairment and patients with <3 months history of renal impairment were excluded. The CKD cases were selected by consecutive sampling and informed consent was obtained. Demographic data, detailed history and clinical examination findings were documented. Height and weight of the patients was recorded and body mass index (BMI) was calculated by formula weight(kg)/ height (m^2).

The serum creatinine levels were obtained. Estimated GFR was calculated by Modification of Diet in Renal Disease (MDRD) formula.[1] The staging of CKD was done by Kidney Disease Outcomes Quality Initiative (KDOQI) classification by national Kidney Foundation.[2] Patients were categorized into CKD stage 1 – 5.

The cardiac evaluation was done on the basis of history, clinical examination, electrocardiography (ECG) and Echocardiography. The degree of cardiac impairment was categorized. Ischemic heart disease was labelled on the basis of history along with ECG, ETT or angiography findings in individual cases.

Data was entered on a specially designed proforma and analyzed by SPSS V-22. Frequencies and percentages were calculated for qualitative variables (i.e., gender, CKD stage); mean and standard deviation were calculated for quantitative variables (age, creatinine, BMI, GFR and cardiac ejection fraction). Chi-square test applied as a test of significance to study the association of eGFR with cardiac ejection fraction. *P-value <0.05* was considered as statistically significant. Data presented as tables and bar graphs.

RESULTS:

Amongst 130 chronic kidney disease cases included in this study, there were 66(51%) males and 64(49%) females. Mean age was 60±13.27 years with a range of 30-87 years. Mean BMI was 24±4.2. Mean monthly income was 25,769±11,676 (10,000-60,000) rupees. Twenty (15.4%) cases were employed, 04(3.1%) were retired and 106(81.5%) were un-employed (table 1).

The most common co-morbid condition observed was hypertension i.e., 122(93.8%), ischemic heart disease in 106(81.5%), diabetes mellitus type 2 in 100(76.9%), congestive cardiac failure in 24(18.5%), Hepatitis C in 13(10%), Hepatitis B and HIV in none of the cases (fig 1).

Various laboratory parameters including mean hemoglobin, renal function tests and electrolytes are presented in Table 1. Mean creatinine level was 4.83±3.53 mg/dl (range 1.2-16) and mean urea was 123.87±66.57 mg/dl (range 39-364). The mean Glomerular filtration rate (GFR) was 17.84±11.33 (2.85-45.18). Total 25(19.2%) patients were receiving the hemodialysis therapy. According to stage of CKD, 73(56.2%) cases were in CKD stage 5, 32(24.6%) cases in CKD stage 4, 22(16.9%) in CKD stage 3 and 03(2.3%) in stage 2. However, we didn't have any patient in CKD stage 1 (table 2).

The mean ejection fraction (EF) of the heart in CKD cases based on echocardiography was 49.18+12.54 % (range 25-65). EF was found to be normal in 39(30%) CKD cases, mildly reduced in 40(30.8%), moderately reduced in 29(22.3%) and severely reduced in 22(16.9%) CKD cases (table 2). Diastolic dysfunction was found in 08(6.2%) CKD patients.

Total 25(18.5%) cases of CKD were diagnosed to have congestive cardiac failure on the basis of history, clinical examination and investigations. Amongst these, 14(56%) cases had compensated CCF and 11(44%) had decompensated CCF. There was significant association between glomerular filtration rate and ejection fraction of the heart ($p<0.0001$).

Table 1: Presenting the demographic variables, anthropometric measurements, electrolytes, renal and cardiac functions (n=130)

Variables		**Mean + SD** (n=130)	**Range**
Age (years)		60.2 ± 13.27	30-87
Monthly income (Rs)		25,769 ± 11,676	10,000-60,000
Height (feet)		5.53 ± 0.247	5-5.8
Weight (kg)		65.18 ± 12.51	40-98
BMI (kg/m^2)		24.27 ± 4.27	17.08-37.55
BP systolic (mmHg)		137.05 ± 20.15	90-180
BP diastolic (mmHg)		83.42 ± 12.49	60-110
Laboratory parameters	Hemoglobin (gm/dl)	10.0 ± 1.65	5.9-14.0
	MCV (fl)	81.28 ± 6.25	60-93
	Urea	123.87 ± 66.57	39-364
	Creatinine	4.83 ± 3.53	1.2-16
	Sodium	131.57 + 15	19-142
	Potassium	4.66 + 0.82	2.3 -7.5
	Calcium	8.84 + 0.72	7.0 – 10.1
	Phosphorus	5.03 + 1.36	2.5-9.4
GFR		17.84 + 11.33	2.85-45.18
Ejection fraction (%)		49.18 + 12.54	25-65

Table 2: Presenting the Ejection fraction grades in various CKD stages (n=13)

CKD Stage	**Normal** (>55%) n=39	**Mildly reduced** (41-55% EF) n=40	**Moderately reduced** (30-40% EF) n=29	**Severely reduced** (<30% EF) n=22	**P-value**
2	**02**	**01**	**00**	**00**	*0.035*
3	**12**	**06**	**02**	**02**	
4	**08**	**15**	**06**	**03**	
5	**17**	**19**	**20**	**17**	

Test of significance Chi-square test; significant p<0.05

Table 3: Presenting the mean GFR and the mean Ejection fraction in CKD cases (n=130)

Variable	**Mean ± SD (n=130)**	**Range**	*P-value*
Glomerular Filtration rate	17.84 ± 11.33	2.85-49.18	*<0.0001*
Ejection Fraction (%)	49.18 ± 12.54	25-65	

Test of significance Chi-square test; p<0.05 significant

Figure 1: Pie Chart presenting the co-morbid conditions in chronic kidney disease cases (n=130).

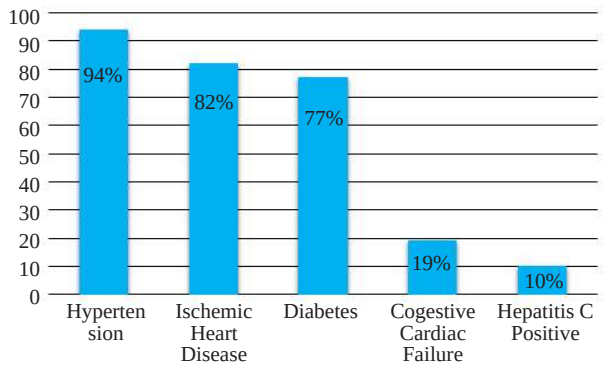
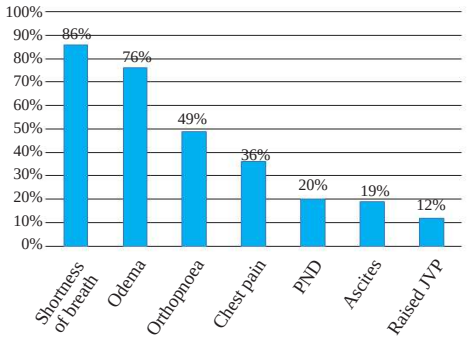


Figure 2: Bar graph presenting various symptoms and signs observed in CKD cases (n=130).



DISCUSSION:

This study finds significant association between left ventricular systolic ejection fraction (LVEF) and the estimated glomerular filtration rate (eGFR). The mean age of the study participants was sixty years with a range of youngest patient of thirty years age and eldest patient eighty-seven years old. Majority of the patients were above fifty years, reflecting the age-related distribution of CKD. Younger patients may develop CKD secondary to congenital hypoplastic kidneys, obstructive uropathy, glomerulonephritis, etc. Certain co-morbid conditions like diabetes, hypertension, pre-renal and post-renal etiologies also lead to CKD.[12]

The body mass index (BMI) was calculated with aim to calculate the eGFR. The mean BMI was twenty-four. Very few CKD cases were overweight or obese. This may be explained by contributory factors like anorexia, ill health, gastro-intestinal malabsorption from gut, loss of muscle mass and wasting in CKD cases.[13] The quality of life needs to be improved by appropriate dietary advise to maintain an appropriate weight in CKD cases. The dietary restrictions and electrolyte abnormalities to be kept in mind while individualizing the diet and caloric intake.[14]

Ten percent of the cases were hepatitis C positive, while none was Hepatitis B positive. The active immunization has contributed to the decline in hepatitis B in our patients. Hepatitis-B immunization is recommended in CKD cases in view of repeated intravenous samplings, intravenous medications and hemodialysis. As these factors increase the risk of exposure to hepatitis B, Hepatitis C and HIV.

Diabetes mellitus has been a predominant contributory factor for CKD in our region. Diabetic nephropathy has been a frequently observed microvascular complication of diabetes. The point to be focused is that with good glycemic control and other preventive measures, the diabetic nephropathy can be avoided or delayed.[15] Approximately seventy seven percent of our cases had diabetes mellitus. This reflects the contribution of diabetes to CKD.

More than ninety percent of our cases were hypertensive. Hypertension and CKD may have varied temporal

association. The hypertension and CKD bear an overlapping cause and effect relationship. Certain cases have hypertensive renal disease leading to CKD. On the other hand, some cases develop hypertension as a consequence of CKD.[16] In either of these situations' early diagnosis and appropriate management of hypertension delays the onset or progression of the CKD. Despite the history of hypertension, most of our patients had therapeutically optimized blood pressures.

Renal anemia is one the most frequent complication of CKD. It involves the decreased endogenous erythropoietin. Most of the study subjects had normochromic normocytic anemia. The KDIGO guidelines state that hemoglobin levels in CKD cases shouldn't be raised above 13gm/dl and the erythropoietin therapy is recommended at hemoglobin < 10 gm/dl, with target hemoglobin 10-11.5 gm/dl.[17]

The gold standard for determining renal functions is GFR.[18] Certain formulas are used worldwide to estimate renal functions including the Cockcroft-Gault formula to estimate the creatinine clearance (CrCl) and, the Modification of Diet in Renal Disease (MDRD) to estimate the glomerular filtration rate (e-GFR).[10] As per the Staging of CKD according to estimated GFR, more than half of our patients were in CKD stage 5 and almost 1/4th in CKD stage 4. We had fewer cases in CKD stage 3 and only three cases in CKD stage 2. The reason may be delay in approach or referral to tertiary healthcare or nephrology. Many patients are referred when the creatinine is already markedly deranged. Hence, authors take the opportunity to convey message from this research that GFR should be calculated for each case of CKD. GFR should be used as basis to evaluate renal function rather than isolated creatinine levels as isolated creatinine may overestimate the renal functions.

While comparing the CKD stages with the cardiac function based on echocardiography-based ejection fraction, we found that more than half of the CKD stage 5 cases had reduced EF. Similarly, reduced EF was found in 3/4th of CKD 4, half of CKD 3 and 1/3rd of CKD 2 cases. There was significant association between the GFR based CKD stage and decline in ejection fraction of heart. Among all cases, thirty percent were found to have preserved ejection fraction vs. seventy percent had reduced ejection fraction. This figure is comparatively higher as compared to Karachi based study by Jameel et al that found low ejection fraction in 31% hemodialysis cases.[19]

The concept is of heart failure with preserved ejection fraction also needs to be discussed. The study conducted by Mavrakanas et al found higher risk of admission in CKD cases having heart failure with preserved ejection fraction (i.e., EF>50%).[20] Hence, this strengthens the recommendation to screen all CKD cases for cardiac dysfunction. This can be done by clinical examination supported by ECG and echocardiography; particularly in CKD stage 3 and above. The earlier stages of CKD should also be monitored as timely intervention may help preserving the cardiac function, hence avoiding the cardiovascular events in CKD cases.

Another interpretation in this study was that amongst cases of heart failure, more than half had compensated heart failure. These cases might not be having overt or obvious symptoms of heart failure and hence their diagnosis of heart failure may be missed. The benefit of diagnosing heart failure will be initiation of preventive therapy for cardiac failure. This may prevent or delay the decline in cardiac function and avoid the cardiac decompensation, acute cardiac events or overt failure.

Certain limitations of the study include sampling technique and inability to perform certain advanced investigations due to financial constraints e.g., basal natriuretic peptides (BNP), cardiac catheterization. Also, we were unable to induct more CKD cases in stage 1 and 2. Hence, results of this study should be interpreted carefully with reference to early stages of CKD. Authors recommend further regional studies with improved sample size and in-depth cardiac evaluation in CKD cases.

CONCLUSION:

The decline in cardiac function is found to be associated with advanced stages of CKD. All the CKD cases are recommended to undergo cardiac evaluation at initial diagnosis and then accordingly at regular intervals. There is high burden of co-morbid conditions particularly diabetes, hypertension, anemia and ischemic heart disease in CKD cases from this region. GFR should be used to estimate the renal functions in CKD cases rather than isolated creatinine levels to avoid errors in the renal function estimation. It is important to diagnose the patients in compensated heart failure and without overt symptoms. This needs high clinical suspicion, supported by investigations. Early intervention may lead to better outcome and reduce the morbidity and mortality.

Authors Contribution:
Nadia Shams: Study design, data collection, write up, data analysis
Muhammad Hussain Baloch: Data collection, write up
Furquana Niaz: Data collection, literature review, write up
Lubna Meraj: Data collection, write up, referencing
Mubarak Ali: Data collection, data entry, write up

REFERENCE:

1. Definition and classification of CKD, Kidney int suppl 2013;3:19. // www.kdigorg / Clinical –practice guideline / pdf / CKD/ KDIGO -2012-CKD –GL.pdf.
2. Nayor M, Larson MG, Wang N, Santhanakrishnan R, Lee DS, Tsao CW, Cheng S, et al. The association of chronic kidney disease and microalbuminuria with heart failure with preserved vs. reduced ejection fraction. Eur J Heart Fail, 2017;19: 615-623. DOI: https://doi.org/10.1002/ejhf.778.
3. Jha V, Garcia G, Iseki K et al. Chronic kidney disease: global Dimensions perspectives. The Lancet. 2013; 382 (9888): 260-272. DOI: https://doi.org/10.1016/S0140-6736(13)60687-X.

4. Jessani S, Bux R, Jafar TH. Prevalence, determinants, and management of chronic kidney disease in Karachi, Pakistan - a community based cross-sectional study. BMC Nephrol. 2014;15:90. DOI: https://doi.org/10.1186/1471-2369-15-90.

5. Jafar TH, Schmid CH, Levey AS. Serum creatinine as marker of kidney function in South Asians: a study of reduced GFR in adults in Pakistan. J Am Soc Nephrol. 2005;16(5):1413-9. DOI: https://doi.org/10.1681/ASN.2004121100.

6. Nayak-Rao S, Shenoy MP. Stroke in Patients with Chronic Kidney Disease. How do we Approach and Manage it? Indian J Nephrol. 2017;27(3):167-171. DOI: https://doi.org/ 10.4103/ 0971-4065.202405.

7. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol. 2008; 52(19):1527-39. DOI: https://doi.org/10.1016/j.jacc.2008.07.051.

8. Hawwa N, Schreiber MJ Jr, Tang WH. Pharmacologic management of chronic reno-cardiac syndrome. Curr Heart Fail Rep. 2013;10(1):54-62. DOI: https://doi.org/ 10.1007/ s11897-012-0122-8.

9. Steenkamp R, Shaw C, Feest T. UK Renal Registry 15th annual report: Chapter 5 survival and causes of death of UK adult patients on renal replacement therapy in 2011: national and centre-specific analyses. Nephron Clin Pract. 2013;123 Suppl 1:93-123. DOI: https://doi.org/10.1159/000353324.

10. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-54. DOI: https://doi.org/10.7326/0003-4819-145-4-200608150-00004.

11. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. Am J Kidney Dis. 2020;76(3 Suppl 1):S1-S107. DOI: https://doi.org/10.1053 /j.ajkd.2020 .05.006.

12. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2021. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2021.

13. Iorember FM. Malnutrition in Chronic Kidney Disease. Front Pediatr. 2018; 6: 161. DOI: https://doi.org/ 10.3389/ fped. 2018.00161.

14. Ikizler TA, Cuppari L. The 2020 updated KDOQI clinical practice guidelines for nutrition in chronic kidney disease. Blood Purification. 2021;50(4-5):667-71. DOI: https://doi.org/ 10.1159/000513698.

15. Fliser D, Wanner C. Precision medicine in diabetic nephropathy and chronic kidney disease. Nephrology Dialysis Transplantation. 2021;36(Supplement_2):10-3. DOI: https://doi.org/10.1093/ndt/gfaa380.

16. Pugh D, Gallacher PJ, Dhaun N. Management of Hypertension in Chronic Kidney Disease. Drugs. 2019;79(4):365-379. DOI: https://doi.org/10.1007/s40265-019-1064-1.

17. Drüeke TB, Parfrey PS. Summary of the KDIGO guideline on anemia and comment: reading between the (guide)line(s). Kidney Int. 2012;82(9):952-60. DOI: https://doi.org/10. 1038/ki.2012.270.

18. Levey AS, Inker LA. GFR as the "gold standard": estimated, measured, and true. American Journal of Kidney Diseases. 2016 ;67(1):9-12. DOI: https://doi.org/10.1053/ j.ajkd.2015. 09.014.

19. Jameel FA, Junejo AM, Khan QUA, Date S, Faraz A, Rizvi SHM, et al. Echocardiographic Changes in Chronic Kidney Disease Patients on Maintenance Hemodialysis. Cureus. 2020; 12(7): e8969. https://doi.org/10.7759/cureus.8969.

20. Mavrakanas TA, Khattak A, Wang W, Singh K, Charytan DM. Association of Chronic Kidney Disease with Preserved Ejection Fraction Heart Failure Is Independent of Baseline Cardiac Function. Kidney Blood Press Res. 2019;44(5):1247-58. https://doi.org/10.1159/000502874.

Original Article **Open Access**

Use of Non-Invasive Ventilation in Reducing Partial Pressure of Carbon Dioxide Level ($PaCO_2$) in Neonates with Respiratory Distress Syndrome

Rida Ali, Shahid Mahmud

ABSTRACT:

Objective: It has been observed that non-invasive ventilation used in premature with Respiratory distress syndrome and notably decrease level of partial pressure of carbon-dioxide ($PaCO_2$) level in blood. The primary goal of this study was to assess the effect of non-invasive ventilation in decreasing the level of partial pressure of carbon dioxide ($PaCO_2$) level and supplementary oxygen need in premature neonates with RDS.

Study Design and Settings: This randomized controlled trial was done in Jan 2021 till August 2021 at PNS SHIFA Karachi.

Methodology: Neonates with gestational age (GA <34 wk) with RDS at birth were randomly assigned to nasal intermittent positive pressure ventilation (NIPPV) and nasal high frequency oscillatory ventilation (NHFOV) for respiratory support after giving surfactant .Twenty three preterm babies were included in each group .Level of partial pressure of carbon dioxide at 2hrs and 24hrs of non-invasive ventilation and supplementary oxygen need was evaluated.

Results: Non-invasive ventilation was found to reduce the $PaCO_2$ level (p= .01), NIPPV (43.06±13.74) vs. (33.63±19.99) in NHFOV at 2hrs and 24hrs NIPPV (19.89±7.18) vs. NHFOV (14.04±8.39).Value of pH was also significant in two groups with optimal mean airway pressure. Supplementary oxygen period were also reduced in NHFOV than NIPPV group (35.7% vs. 64.3%).

Conclusion: NHFOV was a beneficial mode in maintaining level of pH, $PaCO_2$ level and reducing need of supplementary oxygen in preterm babies with RDS.

Keywords: Intermittent Positive-Pressure Ventilation, Respiratory distress syndrome, high-frequency ventilation

How to cite this Article:
Ali R, Mahmud S. Use of Non-Invasive Ventilation in Reducing Partial Pressure of Carbon Dioxide Level (Paco2) in Neonates with Respiratory Distress Syndrome. J Bahria Uni Med Dental Coll. 2022; 11(3):148-151 DOI: https://doi.org/10.51985/JBUMDC2021106

INTRODUCTION:

In neonates transition of pulmonary mechanism just after birth leads to respiratory distress in 7% of preterm babies.[1] There are many causes of respiratory distress, surfactant deficiency is one of the commonest cause of Respiratory distress syndrome among preterm neonates. The immaturity of lungs causes respiratory failure, that leads to decrease in the partial pressure of oxygen (PaO_2) with increment in the partial pressure of carbon-dioxide ($PaCO_2$).[2] The in-sufficiency of lungs cause various morbidities as well as mortality in premature neonates. Mechanical ventilation is the novel respiratory strategy in providing respiratory support. Prolonged use of invasive mechanical ventilation is associated with various ventilator induced complications like volutrauma, chronic lung disease, pneumothorax and bronchopulmunary dysplasia and other morbidity in premature neonates. This has been shown many times, that chronic lung injury can be decreased by reducing time of invasive ventilation. New mode of non–invasive respiratory modes nasal High Frequency Oscillatory Ventilation (NHFOV), Nasal Intermittent Positive Pressure Ventilation (NIPPV), nasal continuous positive airway pressure (NCPAP), are undergoing at present in China to see the trends of respiratory support.[3] A survey has been conducted in European countries which showed that 17% use of nasal HFOV in contrast to NCPAP, in less than 1500 gms premature neonates when nasal CPAP was failed, but it needs time to accept this new strategy.[4]

Nasal High Frequency Oscillatory Ventilation (NHFOV) is superior to other non-invasive ventilation technique in preventing respiratory failure in premature in previous two retrospective studies.[5] Nasal intermittent positive pressure ventilation enhances continuous positive airway pressure along with additional lung inflation at preset peek pressure (15-22 cmH2o), that improves tidal and minute volume with reduced inspiration capacity ,to maintain thoracic wall movement in newborns for better lung compliance.[6]

Rida Ali
Assistant Professor, Paediatrics
PNS SHIFA / Bahria University Medical & Dental College
Email: drrida.ali09@gmail.com

Shahid Mahmud
Head of Department Paediatrics & Neonatal Medicine.
PNS SHIFA / Bahria University Medical & Dental College
Email: childspec@hotmail.com

Received: 17-Nov-2021
Accepted: 16-Jun-2022

Nasal High Frequency Oscillatory Ventilation does not need synchronization and increases rate of carbon-dioxide clearance. There are two justifications for nasal high frequency oscillatory ventilation (NHFOV) in clearance of carbon-dioxide level. The combined features of invasive high frequency oscillations with add-on nasal CPAP is effective in improving lung ventilation by low air trapping in lungs ,even at high pressure and adequate glottis expansion through continuous oscillation, that cause increase CO_2 removal from the lungs.[7] In addition ,laryngeal constriction and distention in abdomen is limited that assists in aeration of lung.[8] On the other end, nasal CPAP is not effective in reducing CO2 successfully due to ineffective oscillation.[9]

Few studies have been done using nasal HFOV and NIPPV mode as a primary respiratory mode. This is the first study to our knowledge that is done in Pakistan using this respiratory support as primarily in neonates .The main objective of this study was to assess the efficacy of non-invasive ventilation as a primary respiratory support, in decreasing the level of partial pressure of carbon-dioxide level ($PaCO_2$) and need of supplementary oxygen ,in premature neonates with respiratory distress syndrome. Our hypothesis was nasal high frequency ventilation will be effective in reducing level of $PaCO_2$ level and decreasing the need of supplementary oxygen.

METHODOLOGY:

A randomized controlled trial was done from March 2021 to Aug 2021 at neonatal unit PNS SHIFA Hospital Karachi. According to Helsinki Declaration, Consent from Ethical review committee was taken (ERC/2021/PED/52), informed consent and permission for publication was taken from parents. Neonates with GA less than 34 wk with clinical signs of respiratory distress syndrome as tachypnea, grunting and nasal flaring were enrolled. Neonates with any pulmonary leak, congenital pneumonia, congenital cardiac defect, cardiopulmonary resuscitation, congenital diaphragmatic hernia, intraventricular bleed, and pulmonary hemorrhage were not enrolled. Open Epi Version 3 software was used for sample size, at 95% confidence interval with 5% margin error. By taking reference study,[10] sample size was taken 23 in each group (NHFOV vs. NIPPV) with total of 46.Neonates with clinical signs of respiratory distress syndrome at birth were randomly given NHFOV and NIPPV with sealed opaque envelopes. Nasal high frequency oscillation (MEDIN Germany) given by nasal mask as per size of nares, settings were frequency 8 (range 8-10) and amplitude 7 (7-10) MAP 6cmH_2O (6-10),non-invasive positive pressure ventilation (CNO-MEDIN Germany) PEEP 6,PIP 15, Rate 45 (40-50),IT 0.40 sec, FiO_2 was maintained to keep SpO_2 90-94% >30wk and 89-93% <30wk.[11] Neonates were given injection Curocef with dose of 2.5 ml per kg with INSURE method followed by second dose of 1.5ml per kg if FiO_2 >40% to keep SpO_2 90-94% in >30 wk and 89-93% in <30 wk before allocation of respiratory support. Patients were weaned off from respiratory support once fiO_2 < 0.25%, MAP < 6 and no sign of respiratory distress. Injection Caffeine 20 mg/ kg loading followed by 10 mg/kg once a day, was given for preterm babies with apnea. Neonates were immediately kept on mechanical ventilator, if hypoxia with severe respiratory distress develop, respiratory acidosis $PaCO_2$ >65 and pH <7.2, apnea with bradycardia and need of cardiopulmonary resuscitation[12,13].

Patient's general characteristics were recorded in a structured Performa by researcher that included, birth weight, gestational age, gender, mode of delivery, antenatal corticosteroid, premature rupture of membrane, signs of RDS.

Primary outcome were decreased level of $PaCO_2$ after 2 hrs and at 24 hrs were checked by (taking capillary blood sample) arterial blood gas machine portable at incubator side. Period of non-invasive ventilation and need of supplementary oxygen in two group's nasal HFOV and NIPPV in preterm with RDS during the admission stay of hospital.

Data analysis was done by SPSS version 19 .Student's *t*-test was applied for continuous data. Chi-squared test was applied for comparison of proportions, student's t-test for continuous data and Fisher's exact test for categorical data. $P < 0.05$ was considered as statistically significant.

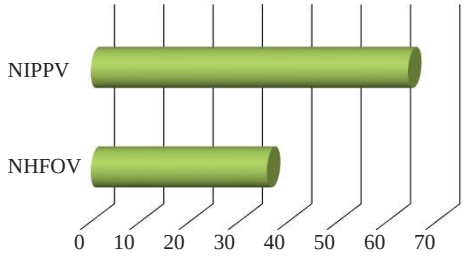
RESULTS:

46 neonates (23 in each group) were enrolled in March 2021 to August 2021 and randomly divided to nasal HFOV and NIPPV group. There was no difference found in the general characteristics of neonates in two groups .The mean Gestational age in weeks (nasal HFOV 29.96±2.38vs NIPPV 43.58±61.03),weight in grams (nasal HFOV 1347±458 vs. NIPPV 1672±534) , male / female ratio (NHFOV 13/11 vs. NIPPV 16 /8), delivered via LSCS nasal HFOV (42.1%) and NIPPV (57.9%) and antenatal corticosteroids were given to (NHFOV 51.1% vs.NIPPV48.9%).Value of pH was stable in NHFOV group (p=.04) at 2 hours and (p=.02) at 24 hours.$PaCO_2$ and HCO_3 was decreased significantly in nasal HFOV than NIPPV group as shown in Table 1.Whereas need of supplementary oxygen in NHFOV was (p=.01) as shown in Fig 1.No difference was found in period of non-invasive ventilation . Mean airway pressure (nasal HFOV 5.72± 0.17 & NIPPV 5.71 ± 0.26 p = 0.44).

Table 1: Outcome Variables

Variables	NHFOV(n=23)	NIPPV(n=23)	p-value
At 2hours			
$PaCO_2$	33.63±19.99	43.06±13.74	.063
HCO3	15.41±8.02	19.82±4.04	.020
At 24 hours			
$PaCO_2$	14.04±8.39	19.89±7.18	.013
HCO3	14.04±8.39	19.89±7.18	.013

Figure 1: Period of Oxygen Supplimentation



DISCUSSION:

Nasal high frequency ventilation was found to be effective in reducing need of invasive mechanical ventilation.[14] Nasal high frequency ventilation was a new respiratory strategy in eliminating CO2.In a retrospective study by Mukerji, showed that nasal HFOV used as an extubation mode in contrast to nasal CPAP in eliminating carbon-dioxide level, decrease apnea episodes, bradycardia and desaturation.[15] Where as, in a randomized crossover trial by Rüegger et al, carbon-dioxide level was not maintained besides premature neonates were given nasal HFOV at 4 hours after giving surfactant.[16]

We applied nasal high frequency oscillatory ventilation as a primary respiratory support, via nasal mask as interface. Our study showed, significant decline in $PaCO_2$ level in nasal HFOV (33.63±19.99) vs. NIPPV (43.06±13.74) after two hours and at 24 hours (14.04±8.39) vs. NIPPV (19.89±7.18), (p =.01) in neonates with GA 27 wk - 34 wk with respiratory distress syndrome. This pattern of lowering CO2 (46.6 ± 7.5 mmHg) on non-invasive high frequency ventilation was also noted in 206 neonates with GA <37wk with RDS after extubation at 6 hours and reduced need of re-intubation ,in a randomized controlled trial by Chen L in 2019.[17] Similar to our study ,Bottino R et al in randomized controlled trial 2018 ,studied that neonates with GA 26.4 ± 1.8 wk and birth weight 921 ± 177 gms , there was decreased partial pressure of carbon-dioxide ($PaCO_2$) in nasal HFOV (49.6 ± 8.7 vs. 56.9 ± 9.9) than nasal CPAP.[18]

In contrast to our study,Colaizy[19]also found reduced level of carbon-dioxide to 45 torr from 50 torr (p=.01) after 2 hours of nasal HFOV in relative similar gestational age of 26-30 wk neonates .Value of pH was also increased 7.40 after two hours of nasal HFOV. In another randomized controlled trial by Wu HL was conducted in 2021 in which infant with cardiac defects at birth ,had low threshold for post extubation respiratory failure post operatively ,as nasal HFOV was contrast reduced $PaCO_2$ in next 12 hours (43.6 ± 7.3 mmHg, p = 0.05)[20], a similar pattern as in our study .In comparison to our study, Danial did not find any difference in elimination of carbon-dioxide level at 4 hours of nasal high frequency oscillatory ventilation than NCPAP in 27 ±2 wk premature neonates,[21] whereas we have found decreased $PaCO_2$ level in nasal HFOV (33.63±19.99) vs. NIPPV (43.06±13.74) after two hours.

Mean airway pressure was remain constant in (nasal HFOV 5.72±0.17 vs. 5.71±0.26 NIPPV) in two groups of our study, in contrast (10.9 ± 2.06) to other previous studies[22].Our study did not show any major difference in the duration of non-invasive ventilation among preterm neonates, however oxygen supplementation was significantly low in nasal HFOV 35.7% than NIPPV 64.3% ,(p= .019).In contrast to NCPAP ,Malakianet al ,was shown contrast difference in duration of non-invasive ventilation in nasal HFOV (p=0.01) among 28 wk till 34 wk GA neonates,[23] whereas no difference in need of mechanical ventilation .Li Y et al stated that nasal HFOV was seen effective in decreasing non-invasive ventilation period, in preterm with GA <34 wk as an extubation respiratory support.[24] Zhu et al also studied the same GA 28WK-34wk as we did in our study ,for nasal HFOV and NCPAP as an initial respiratory support ,mechanical ventilation need was(p<0.01),hence period of non-invasive ventilation was not elicted.[10] It was seen in our study that oxygen supplementation was significantly decreased in nasal HFOV 35.7% than NIPPV 64.3%. Whereasa comparative study by Dursan 2019, using NIPPV vs. nasal CPAP ,didn't show any change in period of oxygen supplements but difference in endotracheal intubation need (p<0.05) in 24wk-32wk neonates.[25]

Nasal HFOV has been used as primordial non invasive respiratory support that was found to reduce the invasive mechanical ventilation need in premature neonate .It has been noted that nasal high frequency ventilation was used as an extubation mode in previous retrospective studies. Whereas in our study nasal high frequency oscillatory ventilation was used as a primary respiratory support in preterm neonates, very few studies in the past use this nasal HFOV as primary respiratory mode. Hence nasal high frequency ventilation was found to be effective respiratory derive in elimination $PaCO_2$, decreasing need of prolong ventilation add on shortening of supplementary oxygen support, besides period of non-invasive ventilation was not found significant in two groups of our study. A beneficial effect of decrease need of oxygen supplements in our study 35.7% as compared to NIPPV 64.3%, that prevent development of bronchopulmunary dysplasia in GA 27-34wk. High frequency ventilation has many aspects that are under observation. In this study we used nasal mask as an interface to deliver nasal HFOV which had been studied in past, but in our study it was effective in reducing $PaCO_2$ and supplementary oxygen requirement.

CONCLUSION:

Nasal high frequency oscillatory ventilation was significantly effective in reducing $PaCO_2$ level and supplementary oxygen demand among preterm with respiratory distress syndrome, that prevents an untoward effects of prolong mechanical ventilation.

Authors Contribution:
Rida Ali: Study Design, Data Collection, Write up
Shahid Mahmud: Literature Review

REFERENCES:

1. Agarwal R, Deorari A, Paul V, Sankar MJ, Sachdeva A. AIIMS Protocols in Neonatology. 2. Delhi: Noble Vision; 2019.
2. Shao XM, Ye HM, Qiu X. Practice of neonatology. People's Medical Publishing House. 2011:115-89.
3. Shi Y, De Luca D, Continuous positive airway pressure (CPAP) vs noninvasive positive pressure ventilation (NIPPV) vs noninvasive high frequency oscillation ventilation (NHFOV) as post-extubation support in preterm neonates: protocol for an assessor-blinded, multicenter, randomized controlled trial. NASalOscillatioN post-Extubation (NASONE) study group.BMCPediatr. 2019; 19(1):256. DOI: 10.1186/s12887-019-1625-1 d
4. Fischer HS, Bohlin K, Bührer C, Schmalisch G, Cremer M, Reiss I et al ,Nasal high-frequency oscillation ventilation in neonates: a survey in five European countries. Eur J Pediatr. 2015;174(4):465-71. DOI: 10.1007/s00431-014-2419-y
5. Wang CH, Shi LP, Ma XL, Lin HJ, Xu YP, Du LZ et al . Use of noninvasive high-frequency oscillatory ventilation in very low birth weight infants].2017; 55(3):177-181.DOI: 10.3760/cma.j.issn.0578-1310.2017.03.003
6. Owen LS, Morley CJ, Davis PG. Nasal intermittent positive pressure ventilation: what do we know in 2007?.Archives of Disease in Childhood. Fetal and Neonatal Edition 2007;92(5):F414-8.DOI: 10.1136/adc.2007.117614
7. Klotz D, Schaefer C, Stavropoulou D, Fuchs H, Schumann S. Leakage in nasal high-frequency oscillatory ventilation improves carbon dioxide clearance-A bench study. PediatrPulmonol. 2017; 52(3):367-372.DOI: 10.1002/ ppul.23 534
8. De Luca D, Piastra M, Pietrini D, Conti G .Effect of amplitude and inspiratory time in a bench model of non-invasive HFOV through nasal prongs. PediatrPulmonol. 2012; 47(10):1012-8. DOI: 10.1002/ppul.22511
9. DiblasiRM .Nasal continuous positive airway pressure (CPAP) for the respiratory care of the newborn infant. .Respir Care. 2009; 54(9):1209-35. PMID: 19712498.
10. Zhu XW, Zhao JN, Tang SF, Yan J, Shi Y .Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with moderate-severe respiratory distress syndrome: A preliminary report..PediatrPulmonol. 2017; 52(8):1038-1042.DOI: 10.1002/ppul.23755
11. Cayabyab R, Arora V, Wertheimer F, Durand M, Ramanathan R. Graded oxygen saturation targets and retinopathy of prematurity in extremely preterm infants. Pediatr Res. 2016; 80(3): 401–406.DOI: 10.1038/pr.2016.98
12. Lista G, Castoldi F, Fontana P, Daniele I, Cavigioli F, Rossi S et al. Nasal continuous positive airway pressure (CPAP) versus bi-level nasal CPAP in preterm babies with respiratory distress syndrome: a randomised control trial. Arch Dis Child Fetal Neonatal Ed. 2010;95(2):F85–F89.DOI: 10.1136/adc.2009.169219
13. O'Brien K, Campell C, Brown L, Wenger L, Shah L. Infant flow biphasic nasal continuous positive airway pressure (BP-NCPAP) vs. infant flow NCPAP for the facilitation of extubation in infants = 1,250 grams: a randomized controlled trial. BMC Pediatr. 2012;12:43–51. DOI: 10.1186/1471-2431-12-43
14. Li J, Li X, Huang X, Zhang Z ,Noninvasive high-frequency oscillatory ventilation as respiratory support in preterm infants: a meta-analysis of randomized controlled trials. Respir Res. 2019; 20(1):58.DOI: 10.1186/s12931-019-1023-0
15. HaidarShehadeh ,Non-invasive high flow oscillatory ventilation in comparison with nasal continuous positive pressure ventilation for respiratory distress syndrome, a literature review. AM J Matern Fetal Neonatal Med. 2021; 34(17):2900-2909. DOI: 10.1080/14767058.2019.1671332
16. Mukerji A, Singh B, Helou SE, Fusch C, Dunn M, Belik J et al , Use of noninvasive high-frequency ventilation in the neonatal intensive care unit: a retrospective review. Am J Perinatol. 2015; 30(2):171-6.DOI: 10.1055/s-0034-1381317
17. Rüegger CM, Lorenz L, Kamlin COF, Manley BJ, Owen LS, Bassler D et al , The Effect of Noninvasive High-Frequency Oscillatory Ventilation on Desaturations and Bradycardia in Very Preterm Infants: A Randomized Crossover Trial.JPediatr. 2018; 201():269-273.e2. DOI: 10.1016/j.jpeds.2018.05.029
18. Bottino R, Pontiggia F, Ricci C, Gambacorta A, Paladini A, Chijenas V et al. Nasal high-frequency oscillatory ventilation and CO2 removal: A randomized controlled crossover trial. PediatrPulmonol. 2018; 53(9):1245-1251.DOI: 10.1002/ppul.24120
19. Colaizy TT, Younis UM, Bell EF, Klein ,Nasal high-frequency ventilation for premature infants. JM ActaPaediatr. 2008; 97(11):1518-22.DOI: 10.1111/j.1651-2227.2008.00900.x
20. Wu HL, Lei YQ, Xie WP, Chen Q, Zheng YR. Nasal High-Frequency Oscillatory Ventilation vs. Nasal Continuous Positive Airway Pressure as Therapy for Postextubation Respiratory Failure in Infants After Congenital Heart Surgery. Front Pediatr. 2021;9:700632.DOI: 10.3389/fped.2021.700632
21. Klotz D, Schneider H, Schumann S, Mayer B, Fuchs H . Non-invasive high-frequency oscillatory ventilation in preterm infants: a randomised controlled cross-over trial. Arch Dis Child Fetal Neonatal Ed. 2018; 103(4):F1-F5.DOI: 10.1136/archdischild-2017-313190
22. Seth S, Saha B, Saha AK, Mukherjee S, Hazra A. Nasal HFOV versus nasal IPPV as a post-extubation respiratory support in preterm infants-a randomised controlled trial. Eur J Pediatr. 2021;180(10):3151-3160. DOI: 10.1007/s00431-021-04084-1
23. Malakian A, Bashirnezhadkhabaz S, Aramesh MR, DehdashtianM .Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome: a randomized controlled trial. J Matern Fetal Neonatal Med. 2020; 33(15): 2601-07. DOI: 10.1080/14767058.2018.1555810
24. Li Y, Wei Q, Zhao D, Mo Y, Yao L, Li L et al. Non-invasive high-frequency oscillatory ventilation in preterm infants after extubation: a randomized, controlled trial. J Int Med Res. 2021;49(2):300060520984915.DOI: 10.1177/ 03000605 2098 4915
25. Dursun M, Uslu S, Bulbul A, Celik M, Zubarioglu U, Bas EK. Comparison of Early Nasal Intermittent Positive Pressure Ventilation and Nasal Continuous Positive Airway Pressure in Preterm Infants with Respiratory Distress Syndrome. J Trop Pediatr. 2019;65(4):352-360. DOI: 10.1093/tropej/fmy058

Original Article **Open Access**

Assessment of Optic Nerve Changes in Patients Receiving Anti-Tuberculosis Drugs at Different Time Interval

Shakila Abbas, Sonia Abdul Sammad, Mariyam Akhtar¸ Syeda Tasneem Zahra, Syeda Najam Gulzar, Ayesha Kiran

ABSTRACT:

Objectives: To assess optic nerve changes in patients receiving anti-tuberculosis drugs and to assess optic nerve changes at different time intervals of therapy.

Study design and settings: Descriptive cross-sectional study was conducted from August 2021 to November 2021 in Madinah Teaching Hospital, Faisalabad.

Methodology: 200 eyes of 100 patients receiving anti-tuberculosis therapy since 2-month, 4-month, 6 month and 8 months were taken. Patients did not have any systemic disease other than Tuberculosis. Indirect Ophthalmoscopy was performed to assess changes in fundus and optic nerve head. Optical Coherence Tomography was performed for assessment of retinal nerve fiber layer thickness and cup to disc ratio. Data was analysed by using descriptive statistics and chi-square test with SPSS version 20.

Results: In 2 months there was 16(66.66%) normal fundus, 8(33.33%) glaucomatous optic disc cupping. In 4 months, there was 12(15.38%) normal fundus, 16(20%) optic atrophy, 16(20%) optic neuropathy, 4.00(5%) optic neuritis and 30(38%) glaucomatous optic disc cupping. In 6 months, there was 7(21%) normal fundus, 4(12.5%) optic atrophy and 21(50%) optic neuropathy. In 8 months, there was 24(36%) optic atrophy, 34(51.5%) optic neuropathy, 4(6%) optic neuritis and 4(6%) Glaucomatous optic dis cupping (P 0.00). Result of this study also shows that retinal nerve fiber layer thickness is normal in 83(41.5%), increase in 4(2.0%) and decrease in 113(56.5%).

Conclusions: This study concluded that anti-tuberculosis drugs responsible for optic nerve changes and severity of optic nerve changes increase when duration of therapy increases.

Key words: Ethambutol, Isoniazid, Optic Neuropathy, Optic Nerve, Tuberculosis

How to cite this Article:
Abbas S, Sammad SA, Akhtar M, Zahra ST, Gulzar SN, Kiran A. Assessment of Optic Nerve Changes in Patients Receiving Anti-Tuberculosis Drugs at Different Time Interval. J Bahria Uni Med Dental Coll. 2022; 11(3):152-156 DOI: https://doi.org/10 .51985/JBUMDC2021125

Shakila Abbas
Lecturer, Department of Optometrist
The University of Faisalabad
Email: Shakila.abbas@tuf.edu.pk

Sonia Abdul Sammad
Optometrist, Department of Optometry
The University of Faisalabad
Email: Poorlittlesoul906@gmail.com

Mariyam Akhtar
Optometrist, Department of Optometry
The University of Faisalabad
Email: mariyamakhtar96@gmail.com

Syeda Tasneem Zahra
Optometrist, Department of Optometry
The University of Faisalabad
Email: zahratasneem59@gmail.com

Syeda Najam Gulzar
Optometrist, Department of Optometry
The University of Faisalabad
Email: razaabbas254@gmail.com

Ayesha Kiran
Lecturer, Department of Optometrist
The University of Faisalabad
Email: Ayesha.kiran@tuf.edu.pk

Received: 22-Dec-2021
Accepted: 24-May-2022

INTRODUCTION:

Tuberculosis is a contagious infection that is caused by "mycobacterium tuberculosis" and spreads from one person to another through an air droplet and person just needs to inhale a few germs to be infected. It is a chronic disease and can be curable and preventable. It can involve more than one part of the body such as the brain, intestine, spine or kidney. [1] It is the first infectious disease declared as a global health emergency by the World Health Organization. In developing countries tuberculosis is the leading cause of mortality and morbidity. Tuberculosis most commonly occurs in the poorest section of the community. It most frequently occurs among people living in crowded areas, poor hygienic condition, poor ventilation and poor nutrition may lead to alteration of the immune system which increases the risk of transmission of disease. WHO estimated globally 10 million cases of tuberculosis in 2019. Tuberculosis kills 1.4 million people which make it the second leading cause of death as compared to the HIV and AIDS. [2] In the world Pakistan has fifth highest tuberculosis prevalence. [3]

Tuberculosis most commonly occurs in the poorest section of the community and it has a well-recognized association

between tuberculosis and poverty. [4] Chemotherapy for tuberculosis was discovered in the 1940s and in the 1980s standardized short courses were adopted for its treatment. It is assumed that it was diminished worldwide but the decline was not observed in developing countries. The implementation of (DOTS) Directly-Observed Therapy has been an advancement in the treatment of tuberculosis. [1] Tuberculosis is treated with first line drugs' including ethambutol isoniazid, rifampin and pyrazinamide and streptomycin. [5] It is difficult for the patient to stick with the treatment in case of long-term therapy, if treatment is discontinued during this time patients do not cure from the disease and they develop drug resistance. WHO endorsed the DOT. There are four drugs that are likely to be efficacious to compose the regimen; out of these at least two are core drugs while the other two are compensation drugs.[6]

The role of core drugs is that in any of its metabolic phase it has the capability to kill mycobacterium tuberculosis while the role of companion drug is that it supports the core drug. The core and the companion drug maintain the entire duration of treatment as one of the core drugs has fine bacteriostatic activity while the other drug should have good sterilizing activity. The drug that has bactericidal activity minimizes the bulk of rapidly growing bacteria, avoid disease progression and decrease infection.[6] In the chemotherapy of tuberculosis ethambutol play an important role although it has various side effects including blur vision, headache dizziness, nausea, breathlessness, swelling of face, numbness and tingling of fingers and toe, rashes, loss of appetite, vomiting and stomach pain. Anti-tuberculosis drugs have adverse effects on visual functions including decreased visual acuity, blur vision, scotomas and reduced ability to detect green and red color. Color vision defect are the initial sign of ocular changes. Even color vision is affected before visual field and visual acuity. [7] Isoniazid has been a key treatment drug since 1952. It has adverse reactions, are hepatotoxicity and neurotoxicity. [8] Optic disc swelling is associated with isoniazid toxicity. Optic nerve is composed of the retina ganglion cells axons. They're distributed in an organized pattern. It is the only tract of the body that is clinically visible and has a cranial cavity. The retina of the eye is the thin layer of tissue continuous posteriorly with the optic nerve. There are approximately 1.2 million ganglion cells per retina and approximately 4-6 cones and 100 rods per ganglion cell. [9]

Pupillary abnormalities are observed in patient receiving antituberculosis drugs. Binocular Indirect Ophthalmoscope is an instrument and it is clinically applicable for the diagnosis and early intervention. With it structure that are lying in the innermost of the globe is visible including retina, optic disc, macula, retinal blood vessels, optic nerve head. [10] Optical coherence tomography (OCT) is an instrument used to see the retina; it is a non-invasive method used to measure the thickness of retinal nerve fiber layer. It provides the cross-sectional view of the retina along with the axial resolution of 8 to 10 micrometer. OCT can identify and measure the loss of retinal nerve fiber layer and measure the changes in thickness of retinal nerve fiber layer. Hence, clinically identifies optic nerve changes in patients and describes ocular changes in early stages caused by the anti-tuberculosis drug which was not visible with the ophthalmoscope. OCT provides two dimensional images of retinal layers by optical scattering. It is used in the detection of a variety of disease. OCT directly corresponds to the histological findings. [11] The rationale of the study is to rule out optic nerve changes during anti-tuberculosis treatment and to educate the community to undergo timely screening while receiving anti-tuberculosis therapy to avoid preventable blindness.

METHODOLOGY:

A descriptive cross-sectional study was conducted from August 2021 to November 2021 in a Medina Teaching Hospital, Faisalabad in which outpatients referred to eye OPD and receiving anti tuberculosis drugs were selected through a non-Probability purposive sampling technique. The research was approved by institutional ethical review board of The University of Faisalabad (TUF/IRB/005/2021). Sample size was calculated from WHO calculator by taking 95% confidence interval and 5% margin of error. The sample size was determined by WHO formula was 200. A total of 100 with 200 eyes of patients, ranging from 16 to 55 years of age were selected. Tuberculosis patients had been already receiving anti tuberculosis treatment since 2-month, 4-month, 6 month and 8 months were included. Patients with ocular pathologies like diabetic retinopathy, hypertensive retinopathy, glaucoma due to another ocular diseases e.g., myopia, systemic diseases other than tuberculosis like migraine, arthritis, multiple sclerosis and taking any systemic medication other than anti-tuberculosis drug were excluded from this study.

After taking written and informed consent, all patients underwent detailed clinical history, examination and investigations. Torch light examination was performed to assess the relative afferent pupillary defect. [12, 13] It is a condition in which when light is shown to the pupil of both eyes then both pupil does not show equal response. Patients seated comfortably and examiner stood at arms length then light was shown at one eye and pupil response was noted and at the same time light was swing to the other eye and response of the other eye was noted. It was noticed that if the both pupil shows equal response or different. Pupils respond differently to light stimuli shown in one eye at a time showed patients had unilateral relative afferent pupillary defect. Relative afferent pupillary defect clearly showed that patient had any defect in optic nerve and light is unable to pass up to occipital lobe safely. Binocular Indirect ophthalmoscopy (MSL model number MSL25C) was performed to assess changes in fundus and optic nerve head. Optic disc and blood vessels of fundus were also assessed.

Indirect ophthalmoscopy was also necessary to check any papillary oedema any change in fundus colour and swelling of the optic disc. Optical Coherence Tomography (NIDEK) was performed for assessment of optic nerve fibers. Optical Coherence Tomography was performed to check the thickness of retinal nerve fiber layer and to access the cup to disc ratio. To perform Optical Coherence Tomography (OCT), the patient was seated comfortably in front of OCT machine, the head rested on head rest to keep it motionless. The patient was simply looked into the lens of device at small, blinking target; the equipment quickly scaned the eye. After that interpretation was performed and diagnosis was made. After the collection of data descriptive statistics and chi-square test was used with P <0.05 was considered and used IBM SPSS-20 version to get a statistical result.

RESULTS:

The total of 200 eyes of 100 patients was included. The study showed that 100(50%) were male and 100(50 %) were females with mean age 32.93**.** Out of 200 eyes of 100 patients, there was 44(17.5%) normal fundus. There was increased frequency of optic neuropathy during anti-tuberculosis therapy as described in Figure 1. The result of this study also shows that relative afferent pupillary defect was positive in 131(65.5%) and negative in 69(34.5%), optic disc color was pinkish orange in 57(28.5%), grey in 37(18.5%) and pale in 106(53%), optic disc shape was oval in 39(19.5 %), horizontally oval in 40(20 %) and round in 121(60.5%), arterial and venous changes shows normal arteries and veins in 83(41.5%), thick in 4(2.0%) and thin in 113(56.5%), optic disc edema is present in 48(24%) and absent in 152(76.0%) patients taking anti tuberculosis drugs.

Assessment of optic nerve changes with different age group was done. 55 patients were assessed having age range of 16-23 in which 11(20%) had normal fundus, 16(29%) had optic atrophy, 8(14%) had optic neuropathy, 8(14%) had optic neuritis, and 12(21%) had glaucomatous optic disc cupping. 43 patients were assessed having age range of 24-31 in which 23(53%) had normal fundus, 12(27%) had optic neuropathy and 8(18%) had glaucomatous optic disc cupping.

44 patients were assessed having age range of 32-39 in which 14(31%) had optic atrophy, 20(45%) had optic neuropathy and 10(22%) had glaucomatous optic disc cupping. 43 patients were assessed having age range of 40-47 in which 8(18%) had optic atrophy, 20(46%) had optic neuropathy and 10(23%) had glaucomatous optic disc cupping. 15 patients were assessed having age range of 48-55 in which 1(6%) had normal fundus, 6(40%) had optic atrophy, 6(40%) had optic neuropathy, and 2(13%) had glaucomatous optic disc cupping. The result of this study shows, as age increase severity of optic nerve changes also increase with p<0.05 (0.00).

Figure 1: Frequency of optic nerve changes in subjects receiving anti-tuberculosis drug

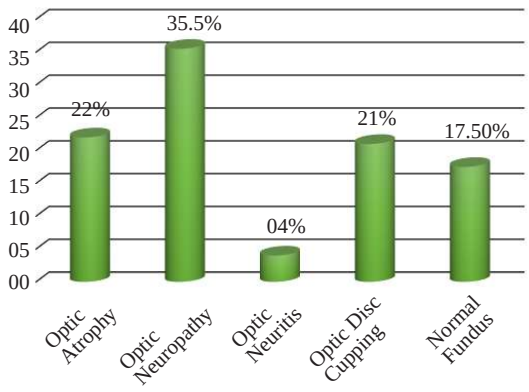


Table 1: Assessment of optic nerve changes with duration of anti-tuberculosis drugs N=200

Duration of therapy	Normal fundus	Glaucomatous optic dis cupping	Optic neuritis	Optic neuropathy	Optic atrophy	P-value
2 months	16 (66.6%)	8 (33.33%)	0	0	0	0.000
4 months	12 (15.38%)	30 (38%)	4 (5%)	16 (20%)	16 (20%)	
6 months	7 (21%)	0	0	21 (50%)	4 (12.5%)	
8 months	0	4 (6%)	4 (6%)	34 (51.5%)	24 (36%)	

Table 2: Assessment of retinal nerve fiber layer thickness with the duration of anti-tuberculosis therapy N=200

Duration of therapy	Normal	Increase	Decrease	P. value
2 months	20(83.33 %)	0	4(16.66 %)	0.000
4 months	38(48.71%)	4(5.12%)	36(46.15%)	
6 months	11(34.37%)	0	21(65.62%)	
8 months	14(21.21%)	0	52(78.78%)	

Comparison of frequency of optic nerve changes with different time intervals of therapy. The result of this study show, as duration increase severity of optic nerve changes also increase with $p<0.05$ as described in Table 1.

For assessment of retinal nerve fiber layer thickness, out of 200 eyes of 100 subjects, the retinal nerve fiber layer thickness was normal in 41.5% (83), increase in 2% (4) and decrease in 56.6% (113).

We compare retinal nerve fiber layer thickness with different time interval of therapy. Results showed that as duration of anti-tuberculosis drugs increases there is decrease in retinal nerve fiber layer thickness with $p< 0.05$ i.e. (0.00) as described in Table 2.

DISCUSSION:

In this study we assess the optic nerve changes due to anti-tuberculosis drugs. Analysis of the optic disc in current study found 19.5% oval, 20.0% horizontally oval and 60.5% round in shape. Arties and veins changes were found 41.5% normal arteries and veins, 2.0% thick arties and veins and 56.5% thin arteries and veins. Optic disc swelling was also observed in 24.0% eyes. Present study also examined Cup to disc ratio. A large number 21% of subjects have increase cup to disc ratio. In previous study they observed optic neuropathy due to ethambutol. They observed ethamnutol cause retibal changes and retinal nerve fiber layer thickness decrease.[14]

The result of present study showed 35.5% patient was optic neuropathy. There were greater chances of optic neuropathy during anti-tuberculosis therapy. Previous study on longitudinal evaluation of subclinical ethambutol induced optic neuropathy was conducted in 2019. They concluded that ethambutol-induced optic neuropathy was found in a total 22 eyes of 14 patients and duration of medication was shown to be a greater risk factor for subclinical toxicity.[15]

Present study explains the parameter that cause visual impairment like glaucomatous disc cupping. Optic nerve is a main point that carries information from retina to brain if any changes occur at this level result visual impairment. Present study observed these changes during treatment periods. 20% optic nerve changing i.e., optic neuropathy occurs at four-month 50% optic nerve changing observed at six month and 51.5% optic nerve changing occur at eight months. In previous study they assessed incidence of visual impairment. According to this study using of anti-tuberculosis drugs 2 to 9 months caused visual impairment in 19.2/1000 persons and permanent visual impairment in 2.3/1000 persons. [16]

A study was conducted on retinal nerve fiber layer analysis in subjects taking anti-tuberculosis therapy. They concluded retinal nerve fiber layer thickness was reduced.[17] The results of present study also showed 56.6% retinal nerve fiber layer loss from optic nerve. Torch light examination was performed to assess pupillary reaction and there was 65.5% positive relative afferent pupillary defect. It will show defect in optic nerve therefore improper information send from optic nerve to brain. There are 21% subjects as cup to disc ratio increases. 53% pale optic disc color was observed.

A study of visual function in subjects on ethambutol therapy for tuberculosis was conducted in 2016. They observe significance difference in visual acuity, fundus changes and visual filed after follow-up of first two months of therapy. [18] Present study result showed that in 2-month therapy (33.33%) have glaucomatous optic disc cupping. At 4-month optic nerve changes were assessed in which 12 patients (15.38%) have normal fundus and 30 patient (38%) have glaucomatous optic disc cupping. Present study describes retinal nerve fiber layer thickness decrease in more (56.5%) then half subjects and increase thickness in few (2.00%) subjects and less (41.5%) then half subjects had normal thickness during eight months of treatment. In present study 12% optic nerve changing in first 2 months of treatment was observed. Optic disc color is grey (18.5%) and pale (53%) and observed disc shape is horizontal oval (20.0%) and round (60.5%). Punit Kumar Singh and Prasnnta in 2020 reported a study and they observed only retinal nerve fiber layer thickness and no remarkable changing observed through ophthalmoscope within starting 2 months of treatment.[19] Present study describes retinal nerve fiber layer thickness decrease in (56.5%) subjects and (41.5%) subjects have normal thickness during treatment. The study had limitation that the time duration was limited and some people did not give complete information related to therapy. Our results coincide with a study on assessment of ocular toxicity in patient receiving ethambutol therapy which was conducted in 2020. They observed significance difference in visual acuity, contrast sensitivity and retinal nerve fiber layer from baseline and first two and six months of treatment. They concluded that retinal nerve fiber layer thickness decreased.[20]

CONCLUSIONS:

The study concluded that there was increased frequency of optic neuropathy as duration of anti-tuberculosis therapy increase. When duration of therapy increases changes become severe. Anti-tuberculosis drugs are responsible for optic nerve changes; patients must undergo optic nerve evaluation and the physician should be fully aware of the diagnosis and clinic evaluation of ocular toxicity caused by anti-tuberculosis drugs, as soon as optic nerve changes are diagnosed intervention should be performed to prevent irreversible blindness.

Authors Contribution:
Shakila Abbas: Concept of study, Conceptualization of study design, data analysis, data interpretation
Sonia Abdul Sammad: Data collection, acquisition of data, data analysis
Mariyam Akhtar: Data collection, acquisition of data, write-up
Syeda Tasneem Zahra: Data collection, write-up
Syeda Najam Gulzar: Literature search, write-up
Ayesha Kiran: Literature search, write-up

REFERENCES:

1. Nitu FM, Olteanu M, Streba CT, Jimborean G, Postolache P, Man MA, et al. Tuberculosis and its particularities in Romania and worldwide. Rom J Morphol Embryol. 2017; 58(2): 385-92.
2. Fukunaga R, Glaziou P, Harris JB, Date A, Floyd K, Kasaeva T. Epidemiology of tuberculosis and progress toward meeting global targets—worldwide, 2019. Morbidity and Mortality Weekly Report. 2021; 70(12):427-430. doi: 10.15585/mmwr.mm7012a4
3. Qadeer E, Fatima R, Yaqoob A, Tahseen S, Ul Haq M, Ghafoor A, et al. Population based national tuberculosis prevalence survey among adults (> 15 years) in Pakistan, 2010–2011. PloS one. 2016;11(2): e0148293. doi.org/10.1371/ journal.pone.0148293
4. Wang L, Zhang H, Ruan Y, Chin DP, Xia Y, Cheng S, et al. Tuberculosis prevalence in China, 1990–2010; a longitudinal analysis of national survey data. The Lancet. 2014; 383(9934):2057-2064. https://doi.org/10.1016/S0140-6736(13)62639-2.
5. Tiberi S, Scardigli A, Centis R, D'Ambrosio L, Munoz-Torrico M, et al. Classifying new anti-tuberculosis drugs: rationale and future perspectives. International Journal of Infectious Diseases. 2017; 56:181-184. https://doi.org/ 10.1016/ j.ijid.2016.10.026
6. Rendon A, Tiberi S, Scardigli A, D'Ambrosio L, Centis R, Caminero JA, et al. Classification of drugs to treat multidrug-resistant tuberculosis (MDR-TB): evidence and perspectives. Journal of thoracic disease. 2016;8(10):2666-2671. doi: 10.21037 /jtd.2016.10.14
7. Abbas A. Monitoring of Side Effects of Anti-Tuberculosis Drugs (ATD) On The Intensive Phase Treatment Of Pulmonary TB Patients In Makassar. Journal of Agromedicine and Medical Sciences. 2017;3(1): 19-24. DOI: https://doi.org/ 10.19184/ams.v3i1.4093
8. Fredj NB, Gam R, Kerkni E, Chaabane A, Chadly Z, Boughattas N, Aouam K. Risk factors of isoniazid-induced hepatotoxicity in Tunisian tuberculosis patients. The pharmacogenomics journal. 2017;17(4):372-377. https://doi.org/10.1038/tpj.2016.26
9. Panchal K et al. Ocular side effects of anti-tubercular drugs in patients receiving Anti-Tb treatment at tertiary care center. IP International Journal of Ocular Oncology and Oculoplasty. 2020;6(3):187-191. DOI:10.18231/j.ijooo.2020.042
10. Solu TM, Panchal KM. Ocular Side Effects of Anti-Tubercular Drugs in Patients Receiving Anti-Tb Treatment at Tertiary Care Center. Journal of dental and medical sciences. 2020; 19(8):9-13. DOI: 10.9790/0853-1908100913
11. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. Progress in retinal and eye research. 2018; 64:1-55. https://doi.org/ 10.1016/j.preteyeres.2017.11.003
12. Saxena R, Singh D, Phuljhele S, Kalaiselvan V, Karna S, Gandhi R, et al. Ethambutol toxicity: Expert panel consensus for the primary prevention, diagnosis and management of ethambutol-induced optic neuropathy. Indian journal of ophthalmology. 2021; 69(12):3734-9. doi: 10.4103/ijo.IJO_3746_20
13. Mandal S, Saxena R, Dhiman R, Mohan A, Padhy SK, Phuljhele S, Sharma P, Guleria R. Prospective study to evaluate incidence and indicators for early detection of ethambutol toxicity. British Journal of Ophthalmology. 2021; 105(7):1024-1028. http://dx.doi.org/10.1136/bjophthalmol-2020-316897
14. Chamberlain PD, Sadaka A, Berry S, Lee AG. Ethambutol optic neuropathy. Current opinion in ophthalmology. 2017 Nov 1;28(6):545-51. DOI: https://doi.org/10.1097 /ICU.0000000000000416.
15. Jin KW, Lee JY, Rhiu S, Choi DG. Longitudinal evaluation of visual function and structure for detection of subclinical Ethambutol-induced optic neuropathy. Plos one. 2019; 14(4):e0215297. doi: 10.1371/journal.pone.0215297
16. Ezer N, Benedetti A, Darvish-Zargar M, Menzies D. Incidence of ethambutol-related visual impairment during treatment of active tuberculosis. The International journal of tuberculosis and lung disease. 2013; 17(4):447-455. doi: 10.5588/ijtld.11.0766.
17. Konnakkodan SM, Solomon CB, Prabhu PB, Kumar AA. Optic nerve head-retinal nerve fiber layer analysis with spectral-domain optical coherence tomography of ethambutol-induced ocular toxicity in patients on a daily regime of anti-tubercular therapy. Kerala Journal of Ophthalmology. 2021; 33(3):291-298. DOI:10.4103/kjo.kjo_162_20.
18. Raghu V, Rajender M, Beesam K, Reddy N. A Prospective evaluation of visual function for early detection of ethambutol toxicity. MRIMS Journal of Health Sciences. 2016; 4(2):89-92. DOI:10.4103/2321-7006.302256
19. Singh PK. The Effect of Anti-Tubercular Drugs on Retinal Nerve Fiber Layer Thickness Using Optical Coherence Tomography. Ophthalmology Research: An International Journal. 2020; 13(1):12-15. DOI: 10.9734/OR /2020/ v13i130157.
20. Bandyopadhyay S, Banerjee S, Bandyopadhyay SK, Shamantha MC, Biswas S. A prospective evaluation of ocular toxicity in patients receiving ethambutol as anti-tubercular therapy. Sudanese Journal of Ophthalmology. 2020; 12(1):12-16. DOI:10.4103/sjopthal.sjopthal_4_20.

Medical Education - Original Article **Open Access**

Assessment of Ideal Learning Style among Medical Students using VARK Learning Approach

Rafia Minhas, Noor Shahid, Zain Gulzar, Sana Zafar, Shahmain Shahzad

ABSTRACT

Objective: Learning styles are important in the learning process so that students can learn in shorter time according to their preferred style. The objective of this study is to observe ideal preferred learning style among medical students and the association of the academic year with the preferred learning style.

Study Design and Setting: A cross-sectional study was conducted at Central Park Medical College, Lahore, Pakistan from September 2021 to December 2021.

Methodology: VARK learning approach was used to identify the ideal learning style. The data was collected using systematic sampling from 148 medical students. The frequency distribution of various preferences of the students was given. Distribution of gender and academic year across their ideal learning style was observed. The association of categorical factors with preferred style was tested using Chi-square test with a level of significance of 5%. SPSS version 26 was used for data analysis.

Results: About 64.8% of the students who participated in the study were female. Nearly 44.6% of the students liked the single modal learning style. Approximately 58% of students prefer K-learning style. Reading was seen as least popular single modal. About 7.4%% of the students liked quad/ multi-modal learning styles.

Conclusion: The most preferred learning style among students was the single learning style. Among single learning styles most of the students preferred kinesthetic followed by aural. The least preferred learning style was found to be quad-modal. Gender and academic year were significant associated factors for preferred learning style.

Keywords: Learning styles, VARK, effective teaching, students

How to cite this Article:
Minhas R, Shahid N, Gulzar Z, Zafar S, Shahzad S. Assessment of Ideal Learning Style among Medical Students using VARK Learning Approach . J Bahria Uni Med Dental Coll. 2022; 11(3):157-161 DOI: https://doi.org/ 10.51985/JBUMDC202234

INTRODUCTION:

Academic achievements and distinctions are the main parameters to access the academic performance of the student. These parameters are influenced by the learning styles. The association between academic performance in education and learning style is still inconclusive. Learning style is the main consideration in designing a teaching methodology. Learning styles and methods used in the learning process. Learning style is the way how a student concentrates, and gain knowledge and experience. When it comes to knowledge gain, memorizing, or recall, students have unique preferences.[1]

Education is a deep process of gaining knowledge, values, habits, and skills whereas learning style is described as the way which is preferred to the students for the acquisition of knowledge, process to memorize or recall.[1,2] The combination of physiological, cognitive, and emotional traits reflects how learner perceive and respond to the environment of learning.[3] It can be summarized based on given definitions that learning style is the preferred way of acquiring knowledge, skills, and experience regarding a subject which must be reliable for understanding, memorizing, and recalling in the future.[4] Organization of the learning process and environment considering learning styles can be effective. In general, learning styles are important in the learning process. Students will be able to learn more in a shorter time if learning process is according to their preferred

Rafia Minhas
Assistant Professor, Department of Medical Education
Central Park Medical College, Lahore
Email: rafiaminhas2005@gmail.com

Noor Shahid
Statistation, Department of Biostatistics
Central Park Medical College, Lahore
Email: noor.shahid.aug@gmail.com

Zain Gulzar
Demonstrator, Department of Medical Education
Fatima Memorial College of Medicine and Dentistry, Lahore
Email: drzaingulzar@gmail.com

Sana Zafar
Demonstrator, Department of Physiology
Central Park Medical College, Lahore
Email: drsana.zaf27@gmail.com

Shahmain Shahzad
Research Scholar, Department of Medical Education
Ripah International University
Email: shahmain1@gmail.com

Received: 14-Mar-2022
Accepted: 20-Jun-2022

learning style. Also, identification of preferred learning styles is important to design an effective curriculum.[2] However, it can be a complex approach to memorizing the concept efficiently and effectively.

A student may have single or multiple learning styles.[5] Each student has their preferred learning style according to which he or she interacts with the learning environment. The basic characteristics of graduate or under-graduate students vary in terms of culture, age, mentality level, smartness, intelligence quotient, and psychological well-being which lead to the variation in preferred learning styles.[1]

Students' ways of thinking and learning styles are the significant aspects to observe the learning outcomes[6]. Most teachers prefer a learning style easy for them ignoring these two aspects.[6,7] The teacher should determine the appropriate approach to be applied in the student-teacher learning process by considering students' way of thinking and learning style.[7] The most familiar learning style of the student should be adopted by the teacher to get maximum learning outcomes. The teacher should identify the preferred learning style of the students. Teachers and students both must update themselves to find the appropriate learning style by mutual consensus.[8]

Over the last decade, students have been shifted from teacher-centered learning to student-centered learning.[3] Students' attention and motivation improve when the facilitator molds the lecture according to their ideal learning style.[8] Various studies have approached to observe the ideal learning style to students. Several methodologies have been adopted. Some tools to observe the preferred learning style were Fleming's VARK Learning Style, Jackson's Learning Styles Profiler (LSP), and Kolb's Learning Style Inventory (LSI). One of the widest approaches is VARK questionnaire. The estimated validation and reliability of the VARK questionnaire were adequate.

VARK questionnaire designed by Fleming and Baume categorizes four taken learning modes into the model i.e. Visual (V), Aural (A), Reading (R), and Kinesthetic (K).[9] Each individual has their own preferred learning style with the individual capability to absorb the lesson. Some are slow learners, some are fast learners, hence they must have a different way to grab lessons and get some information. Visual learners prefer to learn through videos, images, and figures, aural learners prefer to learn through listening to lectures, reading learners likes to read text or notes whereas kinesthetic learners learn through touch and manipulation of objects.[10] The objective of this study was to observe the ideal learning style among medical students and whether there exists an association between the preferred learning style and socio-economic characteristics. As the medical science is a sensitive field and medical curriculum is lengthy,the study aimed to observe the preferred learning style so that in future, learning methodologies can be designed accordingly. These results are also able to generalized to the targeted population of medical students due to the enough and evenly distributed sample size.

METHODOLOGY:

A cross sectional study was conducted at Central Park Medical College from September 2021 to December 2021. The data was collected from 148 medical students in September 2021. The minimum sample size was calculated as 94 with 10% power of the test, 5% level of significance, and 41.6% as the preference of single model learning style.[11] The sample size was quite small but relatively a good representation (nearly one-fourth) of the population of medical students at Central Park Medical College. The study was conducted under the principles of the ethical review committee and approval was obtained from the Institutional Review Board of Central Park Medical College (CPMC/IRB-No/1311). The initial introduction of the learning style and objective of the study was explained to the students and information was collected after their consent the participation. Verbal consent was taken after explanation and written consent was made a part of the given questionnaire.

The inclusion criteria of the investigation were medical students enrolled at Central Park Medical College in MBBS program. Those students with enrollment before 2016 were excluded from the study. Also, those students who refused to participate were excluded from the study. Data was collected using systematic random sampling. A list of all the students enrolled in MBBS was generated and random numbers were assigned. The selected numbers were marked on the list using a systematic random sampling technique. A random start was taken and after every third number, the next student was selected. Selected participants were located on the campus and the objective of the study was explained. Those students who refused to give consent were excluded from the sample.

Data was collected using VARK version 8.01 based on 16-items. VARK tool was used to access the preferred learning style among medical students. VARK was considered as a standard tool for the assessment of the preferred learning styles of the student. The validity and reliability of VARK have been assessed and confirmed in the literature.[12] We used the VARK in the only language. In the literature, it has been transformed in another language such as in the Persian version, and has been psychometrically assessed.[13]

Another section was added to observe the age, gender, academic year, and clinical or pre-clinical year. The reliability of the added section was tested using Cronbach alpha. The reliability was found to be approximately 73%. Frequency distribution of various preferences of the students was given. Distribution of gender and academic year across their ideal learning style was also observed. Association of categorical factors with preferred style was tested using the Chi-square test with a level of significance at 5%. SPSS version 26.0 was used for the data analysis purpose.

RESULTS:

The data was collected from 148 MBBS students in all five years. The mean age of the students was 21.41 + 1.65 SD (in years). The proportion of female students in the sample was comparatively high. About 64.8% of the students who participated in the study were female whereas the rest nearly 35% were male students.

Nearly 44.6%of the students liked a single modal learning style. Among the single modals, students favored kinesthetic (K) followed by aural (A). Approximately 58% of the students prefer the K-learning style. Reading was seen as the least popular single modal. Among the bimodal learning style, approximately 62% of students prefer aural with kinesthetic. About 17.6% of the students choose a tri-modal learning style. About 7.4%% of the students liked the multi-modal learning style.

Female students mostly preferred a single modal learning style followed by a bi-modal (Table 2). Approximately 52% of the male students found single modal as their preferred learning style. About 44.83% of the students in the first-year class, 57.14% of the students in the second year, 44=2.4% of the students in the third-year class, 41.38% of the students in the fourth year, and 37.9% of the students in the final year preferred single-modal style. However, during the academic year wise, most of the students preferred the single-modal learning style preferred by bi-modal.

Chi-square test of association was applied to test the association of gender and academic year with preferred learning style. A 5% level of significance was taken. Gender was observed as a significant factor for preferred learning style with p-values = 0.036. There is statistical significance found between academic year and preferred learning style. The test of means explained that the mean age of participants who prefer various learning styles was approximately the same (p-value >0.05).

Table 1: Preference of VARK learning styles among medical students

Single Modal (n=66)	Bimodal (n=45)	Tri-modal (n=26)	Multi-modal (n=11)
V (n=9)	VA (n=2)	VAR (n=2)	VARK (n=11)
A (n=18)	VR (n=1)	VAK (n=12)	
R (n=5)	VK (n=9)	ARK (n=7)	
K (n=34)	AR (n=2)	VRK (n=5)	
	AK (n=26)		
	RK (n=5)		
n= 66	**n=(45)**	**(n=26)**	**(n=11)**

DISCUSSION:

A large number of studies have been conducted to identify the most ideal learning style near students.[3] The majority of those were conducted during the traditional classroom learning environment phase where interaction between teacher and student was the key aspect to achieve.[1] In recent years, due to the advancement in technology or it would be more appropriate to say that with the support in advance technology in the COVID phase where socialization was limited in an educational institute, the trend of student-teacher learning environment has been shifted.

Both innovation and invention were in relation to technology. As the technology advances, the education system moves towards the adoption of new teaching methodologies. These methodologies were based on using multi-media, audio-visual aid and animated videos during the lecture. These tecahnig methodologies must be designed considering student's preferences. Hence, there is a paradigm shift in the learning choices of students. The major challenge can be the availability of facilities to use the advance technology.

Nowadays a student's learning style is based on not only his understanding but also it considers various factors of which online or on-campus education is the most significant. The dominance of some specific learning styles among students can be influenced by their study domain, teaching methodology, learning experience, the volume of course content, and curriculum content.[10] Therefore, it is highly recommended to the facilitator pay more attention to the variations in learning styles and preferred learning styles among students.[10]

To identify preferred learning styles, the VARK questionnaire is the main approach to improve the teaching quality and learning process.[11] Every student has its own ideal learning

Table 2: Crosstab of gender and academic year with preferred VARK model

Factor	Categories	VARK Modal				Total
		Uni-modal	Bi-modal	Tri-modal	Multi-modal	
Gender	Male	27	13	05	07	52
	Female	39	32	21	04	96
Academic Year	1st Year	13	10	05	01	29
	2nd Year	16	07	02	03	28
	3rd Year	14	12	05	02	33
	4th Year	12	06	09	02	29
	5th Year	11	10	05	03	29

preferrence. With the advancement in technology, students may or may not be attracted to use books.[1] So to enhance the teaching quality and improve the learning process, student's perception for learning methodology must be considered. Learning style and self-awareness lead each student to choose individually their appropriate learning technique. The idea of developing VARK philosophy is that everyone can learn if his/ her distinction is verified. Identifying student's interests will facilitate the teacher to move to the student's learning style from his/ her own teaching methodology and in overcoming the situation where all students tend to prefer specific learning styles.[14] It also helps in the improvement of teaching structure by considering student's point of view.[14]

In our study approximately 45% of the students preferred single modal learning style. Similar to our findings, another study conducted in Iran found that 41.8% of the participants preferred one learning style.[11] Another study conducted by Baykan and Nacar using VARK questionnaire identified the preferred learning styles among one-year medical student and found that 36.1% preferred uni-modal learning style.[15] A study reported the preferred learning styles of two groups of students' i.e. strong students and weak peers. They observe that 47.2% of weak students and 42% of strong students preferred a single learning style.[10] The conclusion was similar to other studies found in literature where the participants preferred a single modal learning style.[3] A study conducted in Pakistan reported that more than 60% of the students preferred multi-modal whereas the remaining 39.37% preferred one of the single modal learning style.[1]

The most preferred single modal learning style was observed as Kinesthetic (K) followed by Aural (A). A recent study done in Pakistan revealed the same conclusion where preferred learning style was Kinesthetic (K) followed by Aural (A).[16] Similar results were found in another study where the preferred learning style was Kinesthetic (K) followed by Visual (V) and Aural (A).[1] In contrast to our results, some studies mentioned that among single modal learning styles, the most preferred style was Aural (A) followed by kinesthetic (K).[17] A similar conclusion was found in other studies conducted in Iran.[4] Visual and Kinesthetic (VK) was found as the most common bi-modal learning style.[3] We observed that Aural and Kinesthetic (AK) was the ideal learning style among bi-modal followed by Visual and Kinesthetic (VK). Among tri-modal learning styles, VAK was seen as the most preferred learning style. Similar findings were found in other studies conducted in Pakistan.[3]

Various studies exist in literature where students preferred multi-modal learning style.[18,19] In our findings, the least preferred learning style was multi-modal or quad-modal. Various studies reported that multi-modal learning style has become the most dominant learning preference.[20,21] In the present research, we observed that gender and preferred learning styles were significantly associated. Quite opposed to our findings another study reported that insignificant difference was found between gender and mean scores obtained from learning styles.[21]

The underlying study was single-centered i.e. conducted in one medical college. No approach was used in the underlying study to observe the ideal learning style rather than the preferred learning style. For that various other associated factors can be tested with preferred learning style such as academic performance of the student and its preferred learning style and the educational outcomes using teaching methodology according to the preferred learning style.

Active learning techniques must be adopted in classroom as they consider various characteristics of learners and are more appropriate and reasonable. Discussion, collaboration, playing roles, stimulating models and active strategies can be utilized. Every student has its own ideal learning preference. This is also important to enhance the teaching quality and improve the learning process, student's perception for learning methodology must be considered. Students will be able to learn more in a shorter time if learning process is according to their preferred learning style. The current study is limited to generalize on the medical colleges in public sector there may be difference in student's ideal learning style due to the available facilities.

CONCLUSION:

The most popular learning style among students was single modal followed by bimodal. Among the bimodal learning style aural together with kinesthetic (AK) was the most popular learning aspect. Multi-modal was the least preferred learning style among students. VARK learning style modal is an effective tool for accessing students' preferred learning styles. As we observed that a single modal learning style is preferred among medical students, there is a need for policymakers to explore the teaching strategies and evaluate the effectiveness to ensure that learners are effectively seeking knowledge. The academic system needs to adopt the teaching methodology according to the student's preferred learning styles.

Authors Contribution:
Raffia Minhas: Study Design, data collection and supervision of study
Noor Shahid: Write-up, data entry and Analysis, Interpretation
Zain Gulzar: Drafting and Proof Reading
Sana Zafar: Data collection, Data Entry
Shahmain Shahzad: Drafting and Final Proof Reading

REFERENCES:

1. Fahim A, Rehman S, Fayyaz F, Javed M, Alam MA, Rana S, Jafari FH, Alam MK. Identification of Preferred Learning Style of Medical and Dental Students Using VARK Questionnaire. BioMed Research International. 2021;2021. DOI: 10.1155/2021/4355158

2. Akhlaghi N, Mirkazemi H, Jafarzade M, Akhlaghi N. Does learning style preferences influence academic performance among dental students in Isfahan, Iran?. Journal of educational evaluation for health professions. 2018;15. DOI: 10.3352/jeehp.2018.15.8

3. Zamani N, Kaboodi A. Evaluation of the VARK model learning styles selection in medical students. Health Res. 2017;2:109-15. DOI: 10.18869/acadpub.hrjbaq.2.2.109

4. Othman N, Amiruddin MH. Different perspectives of learning styles from VARK model. Procedia-Social and Behavioral Sciences. 2010;7:652-60. DOI: 10.1016/j.sbspro.2010.10.088

5. Koohestani HR, Baghcheghi N. A comparison of learning styles of undergraduate health-care professional students at the beginning, middle, and end of the educational course over a 4-year study period (2015–2018). Journal of Education and Health Promotion. 2020;9. DOI: 10.4103/jehp.jehp_224_20

6. Ginting SA. A Facilitating Effective Teaching through Learning Based on Learning Styles and Ways of Thinking. Dinamika Ilmu. 2017;17(2):165-73.

7. Anastas JW. Teaching in social work: An educators' guide to theory and practice. Columbia University Press; 2010 Apr 22.

8. Samarakoon L, Fernando T, Rodrigo C, Rajapakse S. Learning styles and approaches to learning among medical undergraduates and postgraduates. BMC medical education. 2013;13(1):1-6. DOI: 10.1186/1472-6920-13-42

9. Fleming N, Baume D. Learning Styles Again: VARKing up the right tree!. Educational developments. 2006; 7(4):4.

10. Mozaffari HR, Janatolmakan M, Sharifi R, Ghandinejad F, Andayeshgar B, Khatony A. The relationship between the VARK learning styles and academic achievement in Dental Students. Advances in medical education and practice. 2020;11:15. doi: 10.2147/AMEP.S235002

11. Peyman H, Sadeghifar J, Khajavikhan J, Yasemi M, Rasool M, Yaghoubi YM, Nahal MM, Karim H. Using VARK approach for assessing preferred learning styles of first year medical sciences students: a survey from Iran. Journal of clinical and diagnostic research: JCDR. 2014;8(8):GC01. doi.org/10. 7860%2FJCDR% 2F2014%2F8089.4667

12. Zhu HR, Zeng H, Zhang H, Zhang HY, Wan FJ, Guo HH, Zhang CH. The preferred learning styles utilizing VARK among nursing students with bachelor degrees and associate degrees in China. Acta Paulista de Enfermagem. 2018;31:162-9. DOI: 10.1590/1982-0194201800024

13. Mehdipour M, Mortazavi H, Yazdani J, DASTANPOUR S, NAMDARI M, MORADI M. Learning styles of dental students at Shahid Beheshti University of Medical Sciences using VARK questionnaire

14. Wehrwein EA, Lujan HL, DiCarlo SE. Gender differences in learning style preferences among undergraduate physiology students. Advances in physiology education. 2007 Jun 1. DOI: 10.1152/advan.00060.2006

15. Baykan Z, Naçar M. Learning styles of first-year medical students attending Erciyes Universityin Kayseri, Turkey. Advances in physiology education. 2007;31(2):158-60. DOI: 10.1152/advan.00043.2006

16. Mashhood S, Mashhood-uz-Zafar Farooq MF, Fahim MK. Medical student's preferred learning style. Pak J Surg. 2018;34(1):36-40.

17. Aldosari MA, Aljabaa AH, Al-Sehaibany FS, Albarakati SF. Learning style preferences of dental students at a single institution in Riyadh, Saudi Arabia, evaluated using the VARK questionnaire. Advances in medical education and practice. 2018;9:179. DOI: 10.2147/AMEP.S157686

18. Koohestani HR, Baghcheghi N. A comparison of learning styles of undergraduate health-care professional students at the beginning, middle, and end of the educational course over a 4-year study period (2015–2018). Journal of Education and Health Promotion. 2020;9. DOI: 10.4103/jehp.jehp_224_20

19. Ojeh N, Sobers-Grannum N, Gaur U, Udupa A, Majumder MA. Learning style preferences: A study of Pre-clinical Medical Students in Barbados. Journal of advances in medical education & professionalism. 2017;5(4):185.

20. Asiry MA. Learning styles of dental students. The Saudi Journal for Dental Research. 2016;7(1):13-7. DOI: 10.1016/j.sjdr.2015.02.002

21. Al-Saud LM. Learning Style Preferences of First–Year Dental Students at King Saud University in Riyadh, Saudi Arabia: Influence of Gender and GPA. Journal of dental education. 2013;77(10):1371-8

Review Article **Open Access**

Tumor Associated Macrophages: Evolutionary Role in Cancer Therapeutics

Fouzia Fazal, Muhammad Arsalan Khan, Sumayya Shawana, Muhammad Mubarak

ABSTRACT

Cancer therapeutics have evolved more significantly during the last two decades with increasing focus on precision medicine. In principle this involves targeted therapies tailored to patients' cancer-specific molecular attributes. It includes a repertoire of immunomodulating, and apoptotic agents added to cytotoxic chemotherapy, to increase effectiveness. Tumor Associated Macrophages (TAMs) are an interesting potential targets for expanding these therapies. These represent a spectrum of subtypes with anti-inflammatory M1 and pro-tumor M2 being the predominant among all. A large number of studies have established their central role in modulating the tumor microenvironment (TME) and contributing to tumor initiation, and progression. Potential therapeutic strategies that modulate TAMs reduce or block monocyte recruitment, induce apoptosis of TAMs, re-educate TAMs from pro-tumor M2 to anti-tumor M1, among others. This review takes a detailed look at this evolving landscape.

Key Words: Cancer, Tumor associated macrophages (TAMs), Tumor microenvironment (TME) and Precision medicine

How to cite this Article:
Fazal F, Khan MA, Shawana S, Mubarak M. Tumor Associated Macrophages: Evolutionary Role in Cancer Therapeutics. J Bahria Uni Med Dental Coll. 2022; 11(3):162-168 DOI: https://doi.org/ 10.51985/JBUMDC2021109

INTRODUCTION:

Cancer is a multistep process, resulting more commonly with the accumulation of genetic and epigenetic mutations, traversing a number of molecular pathways. In the year 2020 alone, it was responsible for about 10 million deaths worldwide, second only to the ischemic heart disease.[1] Following decades of research, leading to effective screening programs, improved diagnostic modalities and evolving therapeutic strategies, This has led to decreasing mortality associated with, for example, lung, breast, and colorectal cancers. On the flip side, these very cancers still top the yearly incidence, globally.[2] During the last two decades to address this burgeoning challenge, attention has turned toward precision medicine. Tailored to specific molecular attributes of a patient's tumor, focus of cancer therapeutics has shifted from cytotoxic chemotherapy alone to a complex mix of targeted therapies, enabling immunomodulation and apoptosis. Thus, leading to much improved rate of cure and patient survival.[3]

Fouzia Fazal
M.Phil Student, Department of Histopathology
Bahria University Health Sciences
Email: drfozee@gmail.com

Muhammad Arsalan Khan
Professor, Department of Surgery
Sindh Institute of Urology and Transplantation
Email: Muhammad.a.khan@ucdenver.edu

Sumayya Shawana
Professor, Department of Histopathology
Bahria University Health Sciences
Email: shawana75@yahoo.com

Muhammad Mubarak
Professor, Department of Histopathology
Sindh Institute of Urology and Transplantation
Email: drmubaraksiut@yahoo.com

Received: 24-Nov-2021
Accepted: 20-Jun-2022

Defining the role of tumor associated macrophages (TAMs) in cancer biology and its effect on patients' survival, is among the pathways explored by researchers to expand the repertoire of targeted therapies. TAMs are a specialized class of macrophages integrated into the microenvironment of a solid tumor, and through their regulatory molecules like chemokines, cytokines, growth factors and effects on immune checkpoint proteins in the tumor tissue modulate it.[4] The discourse on TAMs has revealed that their varied distribution, and relative densities correlate with cancer prognosis and patients' survival. We also know that biologically TAMs represent an array of subtypes that are modulated by external effector molecular signals. Two of the predominant types, M1 and M2 for instance, have paradoxical antitumor and protumor properties, respectively. The distribution, density and proportion of TAMs and its subtypes evolve with the tumor progression, tipping the balance toward poorer differentiation of cellular and stromal elements. This pathological construct has been validated by several studies demonstrating poor prognosis with the change in TAMs density and increasing M2 proportion in different cancers including breast[5,6], esophageal[7], gastric[8] and colorectal malignancies.[9-11] We have also learned through theoretical modelling and experimental studies, that it is possible to manipulate TAMs, for example by reverting from M2 to M1 state.[12] This has potential implications for efficient management of cancer and represents the focus of the current review.

Coursing through the biology of the tumor microenvironment,

seaming in the role of TAMs in the milieu, we have explored the potential targets these offer and the current state of clinically relevant therapies in the following sections.

The Tumor Microenvironment (TME)

A formative event in the initiation and progression of cancers is the aberrant cellular differentiation that bypasses immunological defenses by modifying the molecular signals and receptors. This tumor cell differentiation is a product of multiple genetic mutations and epigenetic influences like hypermethylation of CpG islands, for instance, in colorectal cancers (CRC). This may result in the mutation into oncogenes or inactivation of tumor suppressor genes, kick-starting the evolution into undifferentiated cancer cells. This is rapidly checked by the tumor microenvironment, a complex interplay of cellular and non-cellular elements surrounding the tumor, in most cases. In a smaller subset it evolves adversely to actually propagate the tumor. We need to look more closely to understand this switch.

The tumor microenvironment's (TME) cellular component includes pericytes, dendritic cells, macrophages, fibroblast and specialized lymphocytes[13], duly alerted by the stromal chemokines and cytokines.[14] The extracellular matrix (ECM) or the non-cellular elements are the structural proteins like collagens and elastin, along with a complex meshwork of glycoproteins like fibronectin and laminins, and the proteoglycans[15] that influence cellular adhesion, as well as modulate cell proliferation, and intercellular communication.[16] Moreover, it harbors humoral elements like transforming growth factor- β (TGF-β), tumor necrosis factor- α (TNF-α) and interleukins (IL-6)[16] that are released on stromal disruption and in turn activate tissue immune cells to attack the abnormal tumor cell. So, the successful tumor progression can only occur if multiple elements (structural, cellular and humoral) of the tumor micro-environment, are abnormally altered. One of the pathways this evolution occurs is through the extracellular vesicles (EVs) like the exosomes, that are released by all the cells of the body, including the tumor cells. Their uptake is receptor dependent and thus directed toward specific cells. Exosomes are endosomal in origin and can transport lipids, proteins as well as RNAs. In the TME, the exosomes secreted by the tumor and immune cells facilitate their effects on each other. Tumor cell-derived exosomes cause inhibition of natural killer and T cells, promote angiogenesis, metastasis and polarization of macrophages and neutrophils to TAMs and tumor associated neutrophils (TANs). This polarization refers to the process induced by various stimuli that transform specific cell lines into distinct functional phenotypes.[17] The transferring of RNA species can reprogram the recipient cell as well. On the other hand, exosomes released by the immune cells can lead to tumor cell apoptosis. A flurry of other effectors work to bypass tissues immune defenses against cancer progression eventually surpassing it and turning it instead in to a tumor promoting microenvironment.

TAMs comprise the main bulk of the infiltrating immune cells in TME in comparison to the dendritic cells, the T cells and the other antigens presenting cells.[18] The tumor microenvironment (TME) determines the change in character, for example, from anti-tumor M1 predominant to pro-tumor M2 dominant macrophage polarization. M2 in turn has been shown to promote all the aspects of TME leading to tumor spread, as mentioned earlier.[4,18]

Tumor Associated Macrophages (TAMs)

Macrophages are white blood cells, derived from the peripheral blood monocytes. Their phagocytic properties, responsible for clearing the cellular debris and tumor cells along with the other harmful foreign agents render them a vital component of mononuclear phagocyte immune system.[19,20] Plasticity and adaptability are the two hallmarks of macrophages.[21] On reaching the tumor, influenced by the immune and tumor cells, the various cytokines and chemokines, possibly the lack of oxygen and the resultant increase in lactic acid, these macrophages evolve into tumor associated macrophages (TAMs).[20]

The role of tumor associated macrophages (TAMs) in cancer tissues is central to understanding this approach for improving cancer therapy. As already mentioned earlier, the macrophages can be classified into two major types depending on their polarization states, i.e., classically activated M1 and alternatively activated M2 macrophages.[20] M1 and M2 macrophages are the two extremes of the polarization spectrum with a number of unaccounted subtypes in between.[17,22]

M1 macrophages are considered pro inflammatory and bactericidal. This polarization state is induced by the factors such as, interferon (IFN) ã and lipopolysaccharides (LPS). M1 macrophages secrete a number of Th1 inducing cytokines like, tumor necrosis factor (TNF) α, interleukin 12 (IL-12), IL-6 and IL-18. These cells have high antigen presenting capacity and also produce reactive oxygen species (ROS), thus are responsible for directly killing the tumor cells.[21,23]

M2 macrophages are immunosuppressive, anti-inflammatory and pro tumor. Their polarization is choreographed by IL-4, IL-13 and IL-10. These cells in turn secrete transforming growth factor (TGF)-β and IL-10, which are responsible for the immunosuppressive nature of tumor microenvironment.[17,23]

In the case of tumors, TAMs highly resemble M2 macrophages, as both are activated in response to the similar cytokines and secrete some common factors, while exhibiting few differences as well.[17] A number of growth factors, cytokines, chemokines and enzymes produced by TAMs play an important role in tumor growth and progression. IL-6 increases the chemoresistance by activating the STAT3 pathway and indirectly increasing the anti-apoptotic protein Bcl2 in colorectal and other solid tumors.[24,25] TAMs promote neovascularization by increased secretion of vascular

endothelial growth factor (VEGF), platelet derived growth factor and TGF β.[26] Matrix metalloproteinases (MMPs) promote invasion and metastasis. TGFβ induces epithelial to mesenchymal transition (EMT) in colorectal cancers through smad/snail signaling pathway.[27] Various chemokines like CCL2, CCL5, including other cytokines and enzymes already mentioned can hinder the CD4+ and CD8+ functions and also result in the recruitment of natural Tregs (nTregs), thus resulting in unsuccessful immunosuppressive therapy.[17]

TAMs as Novel Therapeutic Target for Cancer Immunotherapy

Being an important component of TME, tumor associated macrophages are a desirable target for cancer treatment. TAMs provide multiple potential routes for manipulation with the resultant augmentation of their anti-cancer activity.[28] Reducing or blocking monocyte recruitment into tissues, inducing apoptosis of TAMs already present in the tissue, blocking angiogenesis promoting activities through receptor binding, re-educating or repolarizing TAMs from pro-tumor M2 to anti-tumor M1 type, for example, are some pathways (as summarized in Table 1). Each of these translate to either one of the following anti-tumor effects:[29]

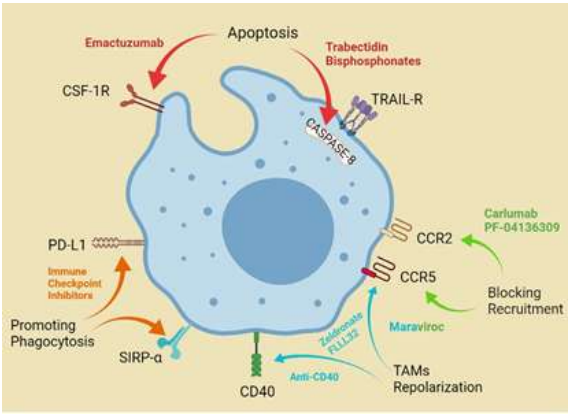
- Direct cellular phagocytosis or cytotoxicity of tumor cells
- Unblocking the cell-death or apoptosis function in tumor cells thus enabling better response to chemotherapeutic agents
- Blocking tumor promoting functions like angiogenesis

In effect this would result in delaying tumor progression or actual tumor regression resulting in improved patient survival. A wholesome volume of research has been directed to these potential targets and its beginning to provide evidence of clinical efficacy.

The therapeutic strategies targeting TAMS, based on experimental research include clearing and inhibiting the activation of TAMS by targeting CSF-1/CSF1R signaling to suppress the tumor growth, promoting the phagocytic activity of macrophages by blocking CD47-SIRPα signaling, limiting monocyte recruitment by targeting CCL2R and inhibition of TAMs by PD-L1 antibody to promote phagocytic activity. Monoclonal antibodies directed against the LILRB1 component of the LILRB1/ MHC class 1 identification mechanism and genetically engineered TAMs lacking the SIRPα and LILRB1 receptors, are few other under trial targets, directed at increasing the phagocytic activity of TAMs.[30] Figure1 graphically demonstrates the currently known agents that target and modulate specific TAMs attributes for potential therapeutic benefit. As promising these treatment options might seem, there is still a long way before they could become a part of regular treatment for solid tumors, as discussed momentarily.

Blocking TAMs Recruitment

Figure1. Specific sites in TAMs that are targeted by various potential agents for therapeutic benefit. For details about these interactions please refer to the related text and table 1.



Blocking TAMs recruitment would theoretically reduce the effect of TAM induced modulation of TME that, although beneficial in initial stages of cancer, are deleterious as tumor progresses. A potential target that triggered significant interest was chemokine CCL2 and its receptor CCR2.[23] A monoclonal antibody against CCL2, carlumab, has been tested in phase I and phase II trials. Although showed encouraging results in the mouse model,[31] and good tolerance in humans, it unfortunately did not translate into therapeutic efficacy as TAM recruitment was not affected among a cohort of prostate cancer patients[32] and a diverse set of solid tumors.[33] Interestingly in combination with FOLFIRINOX (fluorouracil irinotecan plus leucovorin and oxaliplatin) alone, or in combination with CCR2 antagonist as chemotherapy for pancreatic adenocarcinoma,[34] it did lead to TAM depletion in tumors and contributed to partial response in half the patients by hampering tumor growth and metastasis. Among the CRC patients a subset of patients with advanced disease showed encouraging response when Maraviroc, an antagonist to CCR5 receptor of CCL5 chemokine, was used in a preclinical study.[35]

Inducing TAMs depletion

TAMs depletion, already recruited to the tumor, would also potentiate anti-tumor activity in principle, similar to the recruitment blockage paradigm. A wide array of targets and molecules have been employed in basic and clinical research for TAMs depletion.[20] Two of these, namely Bisphosphonates and Trabectidin, are already in clinical use as anti-cancer agents for specific indications. Bisphosphonates are mostly used in patients with bony metastases from solid tumors e.g., breast[36,37] and prostate cancers[38] or against myeloid element in hematological malignancy. As inhibitors of the farnesyl diphosphonate synthase, these tend to accumulate in bone hydroxyapatite where they are taken up by the bone macrophages (osteoclasts), leading to their apoptosis.[39] This macrophage apoptosis is also witnessed non-selectively in non-bony tissues, for example in the liposomal formulation

Table 1. Summary of Potential Pathways for Therapeutic Manipulation of TAMS

Target	Agents	Effect	Tumor Targeted	Effect on ATMs
Clearing/Inhibiting TAMs				
CSF1/CSF1R	PLX3397 (Small molecule inhibitor of CSFIR)	Inhibit the expression of CSFR1	Glioblastoma[50]	Reprogramming into less protumoral phenotype/increa-sed phagocytic ability
CSF1 is involved in macrophage recruitment, repolarization and differentiation (20)	Anti CSF1 antibody	CSF1/CSF1R receptor blockade	Pancreatic ductal adenocarcinoma (PDAC)[51]	Decreased number of TAMs+ selective killing of M2 macrophages
Reducing/ blocking monocyte recruitment				
CCL2/CCR2 inhibition (CCL2 is responsible for recruitment of CCR2 positive macrophages)	PF-04136309 (Small molecule CCR2 inhibitor), in combination with FOLFIRINOX	CCR2 inhibitor	Pancreatic ductal adenocarcinoma (PDAC)[34]	TAM reduction
Inducing apoptosis of TAMs already present in the tissues				
Unspecified (macrophages)	Bisphosphonates (zoledronic acid)	Directly effects macrophages	Breast cancer[39]	Effects macrophage polarization, migration, vesicular trafficking, proliferation and survival
Capase-8 activation	Trabectedin (chemo-therapeutic agent)	Activates caspase-8 – dependent apoptosis	Fibrosarcoma [43, 52]	TAM depletion & reduced angiogenesis
CSFIR inhibition	Emactuzumab (anti CSFIR monoclonal antibody)	Blocks CSFIR activation	Diffuse- type giant cell tumor[42]	TAM depletion
Re-educating/repolarizing TAMs from M2 to M1				
	Biphosphonate (zoledronic acid)	Impaired M2 macrophage polarization	Prostate cancer[48]	Impaired M2 polarization without repolarizing to M1
Macrophage repolarization		Inhibit phosphoryl-ation of STAT3 Inhibits NF-kB canonical pathway	Colorectal cancer[11]	Repolarization of M1 to M2
CCL5/CCLR5 inhibition (CCL5 is a T lymphocyte derived chemokine and affects TAMs)	Maraviroc (Viral entry blocking inhibitor for HIV patients)	CCR5 inhibitor	Colorectal cancer[35]	TAMs repolarization (anti-tumor)
Promoting phagocytic activity of macrophages				
	Hu5F9-G4 (anti CD-47 antibody)	Blocks CD- 47	Non- Hodgkin's lymphoma[53]	Tumor cells phagocytosis

Abbreviations: CSF1: Colony stimulating factor-1,CSF1R: Colony stimulating factor-1 receptor, CCL2: Chemokine (C-C motif) ligand 2, STAT3: Signal transducer and activator of transcription factor 3, NF- kB: Nuclear factor kappa light chain enhancer of activated B cells, CCL5: Chemokine (C-C motif) ligand 5, PDL1: Programed cell- death ligand 1, CD47: Cluster of differentiation 47, SIRPá: Signal regulatory protein alpha

of clodronate, and has found efficacy in reducing visceral as well as bony metastasis in patients with breast cancer. Trabectidin is an alkylating chemotherapeutic drug that is approved for treatment of advanced ovarian cancer,[40] liposarcoma, leiomyosarcoma and other soft tissue sarcomas.[41] Along with its direct cytotoxic effect on neoplastic cells, it has been shown to markedly reduce tissue concentration of TAMs by 30-70% through the TRAIL dependent pathway of apoptosis.[42,43]

Another enticing target to induce TAMs apoptosis has been through the Colony Stimulating Factor-1 (CSF-1) and its receptor CSF1R pathway.[44] This pathway has major role in maturation and differentiation of macrophages and monocytes. Antibodies directed against the CSF1R receptor has been shown in murine models to significantly reduce the number of TAMs in tumor tissue that appears to be more selective for M2 macrophages. Emactuzumab, is the more widely used agent that has been utilized in clinical trials of solid tumors[45,46] like breast, prostate and ovarian cancers. The anti-neoplastic agents commonly used in these tumors

tend to upregulate CSF1/CSF1R complex leading to increasing recruitment, activation and differentiation of macrophages to TAMs, and blocking this pathway has resulted in significant reduction of TAMs population in these tumors even in clinical studies. An alternative to antibody approach has been to utilize tyrosine kinase inhibitor like pexidartinib to block the CSF1 receptor. This has found clinical efficacy and approval in enhancing the response in advanced prostate in combination with hormonal therapy. In general, because of the nonspecific response against macrophages throughout the body, these present a lot of side effects and further work is being directed toward agents that would provide selectivity for M2 macrophages in tumor tissues by targeting for example CD-163 receptors for cell selection.

Reeducating TAMs: M2 to M1

Utilizing TAMs plasticity i.e., ability of converting to M2 from M1 phenotype and vice versa provide other potential means to influence TME. Reeducating M2 to M1 would the antitumor potential and may potentially improve patient survival.[11,47] Alternatively, preventing M1 conversion to M2 may also achieve this goal by preventing pro-tumoral effects of M2. This construct is still in the realm of experimental or preclinical studies. There are a host of theoretical pathways to achieve that and an increasing number of candidate drugs to modulate these pathways. An example is Zoledronic acid and its effects on TAMs repolarization from M2 to M1.[48] An indirect clinical correlation was provided by Gnant et al., through their clinical trial with addition of Zoledronic Acid to endocrine therapies among 1803 premenopausal breast cancer patients, as part of ABCSG-12 randomized trial, was shown to achieve improved survival.[49] More commonly experimental models focus on STAT3 and NF-êB pathways disruption, using for example antibodies like anti-CD 40 antibody, or designer molecules, e.g., FLLL32, a diketone analogue of curcumin to achieve repolarization.[11]

TAMs Manipulation: other alternatives

Alternative strategies, mentioned earlier, that promote the phagocytic activity of macrophages by blocking CD47-SIRPα signaling, inhibition of TAMs by PD-L1 antibody to promote phagocytic activity, monoclonal antibodies directed against the LILRB1(Leucocyte immunoglobulin like receptor subfamily B member 1) component of the LILRB1/ MHC class 1 identification mechanism and genetically engineered TAMs lacking the SIRPα and LILRB1 receptors, are few other strategies for TAMs manipulation.[30] Most of these are still a long way from clinical utility though and mostly experimental constructs at this time. Table 1 summarizes the pathways, targets and agents that researchers have utilized for therapeutic manipulation of TAMs.

CONCLUSION:

Tumor Associated Macrophages represents the most prevalent stromal cell type in the tumor microenvironment. Several studies have demonstrated evolution of their anti-tumoral role as the M1 subtype, polarizing to the other end of the spectrum, the M2 or the protumor subtype, as the cancer progresses. These have multitude of effects on the element of TME like inducing chemoresistance, reducing apoptosis, increasing tumor vascularity, decreasing inter-cellular adhesion, promoting invasiveness and diminishing the response by cytotoxic immune cells. With the advent of targeted therapies in the treatment of cancers, there is increasing focus on targeting TAMs to improve prognosis. Work is ongoing on novel strategies with specific molecular targets that reduce monocyte recruitment, cull TAMs already present in the TME, reeducate TAMs from protumor M2 to antitumor M1 subtype, and promote phagocytosis by TAMs. Some of these have already entered different phases of clinical trials. With a lot of promise and concerted research focus, there is high expectation that TAMs will provide an effective platform to improve cancer therapy in the coming years.

Authors Contribution:
Fouzia Fazal: Conception, Design, Manuscpt.
Muhammad Arsalan Khan: Conception, Design, Manuscpt.
Sumayya Shawana: Critical Analysis
Muhammad Mubarak: Critical Analysis

REFERENCES

1. Mattiuzzi C, Lippi G. Current Cancer Epidemiology. J Epidemiol Glob Health. 2019;9(4):217-222. doi:10.2991/jegh.k.191008.001
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660
3. Erickson AW, Ghodrati F, Habbous S, et al. HER2-targeted therapy prolongs survival in patients with HER2-positive breast cancer and intracranial metastatic disease: a systematic review and meta-analysis. Neuro-Oncology Advances. 2020;2(1)doi:10.1093/noajnl/vdaa136
4. Lin Y, Xu J, Lan H. Tumor-associated macrophages in tumor metastasis: biological roles and clinical therapeutic applications. J Hematol Oncol. 2019;12(1):76. doi:10.1186/s13045-019-0760-3
5. Jeong H, Hwang I, Kang SH, Shin HC, Kwon SY. Tumor-Associated Macrophages as Potential Prognostic Biomarkers of Invasive Breast Cancer. J Breast Cancer. Mar 2019;22(1):38-51. doi:10.4048/jbc.2019.22.e5
6. Yang M, Li Z, Ren M, et al. Stromal Infiltration of Tumor-Associated Macrophages Conferring Poor Prognosis of Patients with Basal-Like Breast Carcinoma. J Cancer. 2018;9(13):2308-2316. doi:10.7150/jca.25155
7. Hu JM, Liu K, Liu JH, et al. CD163 as a marker of M2 macrophage, contribute to predicte aggressiveness and prognosis of Kazakh esophageal squamous cell carcinoma. Oncotarget. 2017;8(13):21526-21538. doi:10.18632/ oncotarget .15630
8. Yin S, Huang J, Li Z, et al. The Prognostic and Clinico-pathological Significance of Tumor-Associated Macrophages in Patients with Gastric Cancer: A Meta-Analysis. PLoS One. 2017;12(1):e0170042. doi:10.1371/journal.pone.0170042

9. Yang C, Wei C, Wang S, et al. Elevated CD163(+)/CD68(+) Ratio at Tumor Invasive Front is Closely Associated with Aggressive Phenotype and Poor Prognosis in Colorectal Cancer. Int J Biol Sci. 2019;15(5):984-998. doi:10.7150/ijbs.29836
10. Krijgsman D, De Vries NL, Andersen MN, et al. CD163 as a Biomarker in Colorectal Cancer: The Expression on Circulating Monocytes and Tumor-Associated Macrophages, and the Soluble Form in the Blood. Int J Mol Sci. 2020;21(16) doi:10.3390/ijms21165925
11. Zhao Y, Ge X, Xu X, Yu S, Wang J, Sun L. Prognostic value and clinicopathological roles of phenotypes of tumour-associated macrophages in colorectal cancer. J Cancer Res Clin Oncol. 2019;145(12):3005-3019. doi:10.1007/s00432-019-03041-8
12. Yahaya MAF, Lila MAM, Ismail S, Zainol M, Afizan N. Tumour-Associated Macrophages (TAMs) in Colon Cancer and How to Reeducate Them. J Immunol Res. 2019;2019: 2368249. doi:10.1155/2019/2368249
13. Labani-Motlagh A, Ashja-Mahdavi M, Loskog A. The Tumor Microenvironment: A Milieu Hindering and Obstructing Antitumor Immune Responses. Front Immunol. 2020;11:940. doi:10.3389/fimmu.2020.00940
14. Yuan Y, Jiang Y-C, Sun C-K, Chen Q-M. Role of the tumor microenvironment in tumor progression and the clinical applications (Review). Oncol Rep. 2016/05/01 2016;35(5): 2499-2515. doi:10.3892/or.2016.4660
15. Wei R, Liu S, Zhang S, Min L, Zhu S. Cellular and Extracellular Components in Tumor Microenvironment and Their Application in Early Diagnosis of Cancers. Analytical Cellular Pathology. 2020/01/08 2020;2020:6283796. doi:10.1155 /2020 /6283796
16. Arneth B. Tumor Microenvironment. Medicina (Kaunas). 2019;56(1)doi:10.3390/medicina56010015
17. Baghban R, Roshangar L, Jahanban-Esfahlan R, et al. Tumor microenvironment complexity and therapeutic implications at a glance. Cell Communication and Signaling. 2020/04/07 2020;18(1): 59. doi:10.1186/s12964-020-0530-4
18. Chen Y, Song Y, Du W, Gong L, Chang H, Zou Z. Tumor-associated macrophages: an accomplice in solid tumor progression. J Biomed Sci. 2019;26(1):78. doi:10.1186/s12929-019-0568-z
19. Yona S, Gordon S. From the Reticuloendothelial to Mononuclear Phagocyte System – The Unaccounted Years. Review. Frontiers in Immunology. 2015-July-01 2015;6(328)doi:10.3389/fimmu.2015.00328
20. Zhou J, Tang Z, Gao S, Li C, Feng Y, Zhou X. Tumor-Associated Macrophages: Recent Insights and Therapies. Front Oncol. 2020;10:188. doi:10.3389/fonc.2020.00188
21. Guttman O, C. Lewis E. M2-like macrophages and tumor-associated macrophages: overlapping and distinguishing properties en route to a safe therapeutic potential. Integrative Cancer Science and Therapeutics. 2016;3(5) doi:10. 15761 /icst.1000204
22. Jayasingam SD, Citartan M, Thang TH, Mat Zin AA, Ang KC, Ch'ng ES. Evaluating the Polarization of Tumor-Associated Macrophages Into M1 and M2 Phenotypes in Human Cancer Tissue: Technicalities and Challenges in Routine Clinical Practice. Front Oncol. 2019;9:1512. doi:10.3389/fonc.2019.01512
23. Pinto ML, Rios E, Duraes C, et al. The Two Faces of Tumor-Associated Macrophages and Their Clinical Significance in Colorectal Cancer. Front Immunol. 2019;10:1875. doi:10 .3389/fimmu.2019.01875
24. Xu X, Ye J, Huang C, Yan Y, Li J. M2 macrophage-derived IL6 mediates resistance of breast cancer cells to hedgehog inhibition. Toxicol Appl Pharmacol. 2019;364:77-82. doi:10. 1016/j.taap.2018.12.013
25. Yin Y, Yao S, Hu Y, et al. The Immune-microenvironment Confers Chemoresistance of Colorectal Cancer through Macrophage-Derived IL6. Clinical Cancer Research. 2017;23(23):7375-7387. doi:10.1158/1078-0432.Ccr-17-1283
26. Tamura R, Tanaka T, Yamamoto Y, Akasaki Y, Sasaki H. Dual role of macrophage in tumor immunity. Immunotherapy. Aug 2018;10(10):899-909. doi:10.2217/imt-2018-0006
27. Cai J, Xia L, Li J, Ni S, Song H, Wu X. Tumor-Associated Macrophages Derived TGF-â-Induced Epithelial to Mesenchymal Transition in Colorectal Cancer Cells through Smad2,3-4/Snail Signaling Pathway. Cancer Res Treat. Jan 2019;51(1):252-266. doi:10.4143/crt.2017.613
28. Yang L, Zhang Y. Tumor-associated macrophages: from basic research to clinical application. Journal of Hematology & Oncology. 2017/02/28 2017;10(1):58. doi:10.1186/s13045-017-0430-2
29. Anfray C, Ummarino A, Andón FT, Allavena P. Current Strategies to Target Tumor-Associated-Macrophages to Improve Anti-Tumor Immune Responses. Cells. 2019;9(1) doi:10.3390/cells9010046
30. Barkal AA, Weiskopf K, Kao KS, et al. Engagement of MHC class I by the inhibitory receptor LILRB1 suppresses macrophages and is a target of cancer immunotherapy. Nat Immunol.2018;19(1):76-84.doi:10.1038/s41590-017-0004-z
31. Sanford DE, Belt BA, Panni RZ, et al. Inflammatory Monocyte Mobilization Decreases Patient Survival in Pancreatic Cancer: A Role for Targeting the CCL2/CCR2 Axis. Clinical Cancer Research. 2013;19(13):3404-3415. doi:10.1158/1078-0432.Ccr-13-0525
32. Pienta KJ, Machiels J-P, Schrijvers D, et al. Phase 2 study of carlumab (CNTO 888), a human monoclonal antibody against CC-chemokine ligand 2 (CCL2), in metastatic castration-resistant prostate cancer. Investigational New Drugs. 2013/ 06/01 2013;31(3):760-768. doi:10.1007/s10637-012-9869-8
33. Brana I, Calles A, LoRusso PM, et al. Carlumab, an anti-C-C chemokine ligand 2 monoclonal antibody, in combination with four chemotherapy regimens for the treatment of patients with solid tumors: an open-label, multicenter phase 1b study. Target Oncol. 2015;10(1):111-23. doi:10.1007/s11523-014-0320-2
34. Nywening TM, Wang-Gillam A, Sanford DE, et al. Targeting tumour-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase 1b trial. The Lancet Oncology. 2016;17(5):651-662. doi:10.1016 /s1470-2045(16)00078-4
35. Halama N, Zoernig I, Berthel A, et al. Tumoral Immune Cell Exploitation in Colorectal Cancer Metastases Can Be Targeted Effectively by Anti-CCR5 Therapy in Cancer Patients. Cancer Cell. 2016;29(4):587-601. doi:10.1016/j.ccell.2016.03.005

36. Diel IJ, Solomayer EF, Costa SD, et al. Reduction in new metastases in breast cancer with adjuvant clodronate treatment. N Engl J Med. 1998;339(6):357-63. doi:10.1056/ nejm199808063390601
37. Powles T, Paterson S, Kanis JA, et al. Randomized, Placebo-Controlled Trial of Clodronate in Patients With Primary Operable Breast Cancer. Journal of Clinical Oncology. 2002;20 (15):3219-3224. doi:10.1200/jco.2002.11.080
38. Macherey S, Monsef I, Jahn F, et al. Bisphosphonates for advanced prostate cancer. Cochrane Database Syst Rev. Dec 26 2017;12(12):Cd006250. doi:10.1002/ 14651858. CD006 250.pub2
39. Junankar S, Shay G, Jurczyluk J, et al. Real-time intravital imaging establishes tumor-associated macrophages as the extraskeletal target of bisphosphonate action in cancer. Cancer Discov. 2015;5(1):35-42. doi:10.1158/2159-8290.Cd-14-0621
40. Ventriglia J, Paciolla I, Cecere SC, et al. Trabectedin in Ovarian Cancer: is it now a Standard of Care? Clin Oncol (R Coll Radiol). Aug 2018;30(8):498-503. doi:10. 1016/j.clon. 2018.01.008
41. Gordon EM, Sankhala KK, Chawla N, Chawla SP. Trabectedin for Soft Tissue Sarcoma: Current Status and Future Perspectives. Adv Ther. 2016;33(7):1055-71. doi:10.1007/ s12325-016-0344-3
42. Ries CH, Cannarile MA, Hoves S, et al. Targeting tumor-associated macrophages with anti-CSF-1R antibody reveals a strategy for cancer therapy. Cancer Cell. 2014;25(6):846-59. doi:10.1016/j.ccr.2014.05.016
43. Germano G, Frapolli R, Belgiovine C, et al. Role of macrophage targeting in the antitumor activity of trabectedin. Cancer Cell. 2013;23(2):249-62. doi:10.1016/j.ccr.2013.01.008
44. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol. 2017;14(7):399-416. doi:10. 1038/nrclinonc.2016.217
45. Machiels J-P, Gomez-Roca C, Michot J-M, et al. Phase Ib study of anti-CSF-1R antibody emactuzumab in combination with CD40 agonist selicrelumab in advanced solid tumor patients. Journal for ImmunoTherapy of Cancer. 2020;8(2): e001153. doi:10.1136/jitc-2020-001153
46. Gomez-Roca CA, Italiano A, Le Tourneau C, et al. Phase I study of emactuzumab single agent or in combination with paclitaxel in patients with advanced/metastatic solid tumors reveals depletion of immunosuppressive M2-like macrophages. Ann Oncol. 2019;30(8):1381-1392. doi:10.1093/ annonc/ mdz163
47. van Dalen FJ, van Stevendaal M, Fennemann FL, Verdoes M, Ilina O. Molecular Repolarisation of Tumour-Associated Macrophages. Molecules. 2018;24(1)doi: 10.3390/ molecules24010009
48. Giuseppina Comito1 CPS, Maria Letizia Taddei1, Michele Lanciotti3 Sergio Serni3, AM, Paola Chiarugi1,2 , Elisa Giannoni1. Zoledronic acid impairs stromal reactivity by inhibiting M2-macrophages polarization and prostate cancer-associated fibroblasts. Oncotarget, 2017, Vol 8, (No 1), pp: 118-132. 2016;
49. Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. The Lancet Oncology. 2011;12(7):631-641. doi:10.1016/s1470-2045(11)70122-x
50. Yan D, Kowal J, Akkari L, et al. Inhibition of colony stimulating factor-1 receptor abrogates microenvironment-mediated therapeutic resistance in gliomas. Oncogene. 2017; 36(43):6049-6058. doi:10.1038/onc.2017.261
51. Zhu Y, Knolhoff BL, Meyer MA, et al. CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models. Cancer Res. 2014;74(18):5057-69. doi:10. 1158/0008-5472.Can-13-3723
52. Liguori M. BC, Pasqualini F., Bergomas F., Pesce S., Sironi M., Grizzi F., Mantovani A., Belgiovine C., Allavena P. Functional TRAIL receptors in monocytes and tumor-associated macrophages: . Functional TRAIL receptors in monocytes and tumor-associated macrophages: A possible targeting pathway in the tumor microenvironment. Oncotarget. 2016; 7: 41662-41676.
53. Advani R, Flinn I, Popplewell L, et al. CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin's Lymphoma. N Engl J Med. 2018;379(18):1711-1721. doi:10.1056/ NEJMoa 1807315
54. Gordon SR, Maute RL, Dulken BW, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. Nature. 2017;545(7655):495-499. doi:10.1038/nature22396

Case Report

Open Access

Cystic Esophageal Gastrointestinal Stromal Tumor (GIST): A Rare Presentation

Junaid Iqbal, Sadia Rashid, Hina Pathan, Sorath Murtaza

ABSTRACT

Gastrointestinal stromal tumors (GIST) are solid tumors of the gastrointestinal tract. The stomach is the most common site while the esophagus is the least common site for gastrointestinal stromal tumors. The cystic Gastrointestinal stromal tumor has never been reported in the past. On CT scan of a young male patient, we reported an exophytic cystic structure of 2.5 x 2.2 cm along the esophagus as an esophageal duplication cyst then he underwent an image-guided biopsy that finally turned out to be a Gastrointestinal stromal tumor on histopathology. He underwent surgical resection; he is now symptoms-free and on 6 monthly CT scan follow-ups.

How to cite this Article:
Iqbal J, Rashid S, Pathan H, Murtaza S. Cystic Esophageal Gastrointestinal Stromal Tumor (GIST): A Rare presentation. J Bahria Uni Med Dental Coll. 2022; 11(3):169-171 DOI: https://doi.org/ 10.51985/JBUMDC202139

INTRODUCTION:

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. They account for up to 3% of all GIT tumors and up to 5.7% of sarcomas.[1] GIST arises from any part of the gastrointestinal tract (GIT), the most common site is stomach followed by the small bowel, colon, and rectum. The esophagus is the least common site, accounting for <1% of all GISTs.[1, 2, 3] The annual incidence of gastrointestinal stromal tumors is 7 to 20 per million. Esophageal GISTs occurred significantly more frequently in men, as well as in patients younger than 60 years at diagnosis. The most common location for esophageal GISTs is the lower esophagus, followed by the middle esophagus , whereas GISTs in the upper esophagus are rare. The clinical features of esophageal GISTs are not well-known due to rarity of esophageal GIST. [4]

The literature on esophageal GISTs is limited, mainly comprising case reports and only a few case series.[1]

CASE PRESENTATION:

Junaid Iqbal
Assistant Professor, Department of Radiology
Ziauddin Hospital, Karachi
Email: junaid2008@gmail.com

Sadia Rashid
Consultant, Department of Radiology
Patel Hospital, Karachi
Email: dr_sadiarashid@yahoo.com

Hina Pathan
Senior Registrar, Department of Radiology
Ziauddin Hospital, Karachi
Email: hn_pathan@yahoo.com

Sorath Murtaza
Consultant, Department of Radiology
Ziauddin Hospital, Karachi
Email: Sorathmurtaza@gmail.com

Received: 14-Jun-2021
Accepted: 11-Apr-2022

A 35-year-old male came to OPD with chest pain, dysphagia, and odynophagia for two months. CT scan was done which showed an exophytic cystic lesion along the right posterolateral wall of the cervical esophagus. It was a well-defined hypodense mass not showing enhancement on post-contrast images (Fig 1 & 2 white arrow), measuring 2.5 x 2.2 cm. Initially it was diagnosed as a duplication cyst. MRI was done as presurgical planning which showed well defined exophytic lesion. It was hypointense on T1W, slightly hyperintense on T2W, and showed minimal enhancement on post-contrast images (Fig 3 & 4 white arrowhead). Endoscopy was not performed as the patient did not give consent. Due to minimal enhancement, an ultrasound-guided trans-thyroid biopsy was performed and it came out to be an esophageal gastrointestinal stromal tumor (GIST), spindle cell type with the expression of Ki67 and CD117 on histopathology. The patient underwent an esophagectomy with end-to-end anastomosis. The tumor did not involve the esophageal sphincter and was located approximately 15 cm proximal to the gastro esophageal junction. The histopathology of the surgical specimen showed that, it is low-grade gastrointestinal stromal tumor (GIST). He recovered and was discharged successfully after 8 days. He is currentlyon imatinib (tyrosine kinase inhibitor). The patient is now asymptomatic and is on 6 monthly follow-up.

DISCUSSION:

Gastrointestinal stromal tumors (GISTs) were previously classified as smooth muscle tumors but now proved that they arise from the interstitial cells of Cajal and on immunohistochemistry they express KIT protein-CD117. GIST can arises from any part of the gastrointestinal tract (GIT) including the omentum. They usually originate from the muscularis propria. The tumor growth is exophytic rather than intraluminal or intramural.[5]

GISTs of the esophagus are usually asymptomatic especially when they are small but as the tumor grows, patients present

with different symptoms due to pressure effects like dysphagia, chest pain, reflux, and heartburn[6]. Larger tumors may cause obstruction of the gastrointestinal lumen.[7] GISTs are usually reported in middle-aged and elderly people, and they range in size from sub centimeters up to 40cms.[8] Smaller GISTs (< 2cm) have almost no chance of invasion or infiltration, however, GIST cannot be labeled as benign.[9] On Computed Tomography scan, GISTs appear as a large exophytic, hypervascular, enhancing solid mass and sometimes appear heterogeneous due to necrosis, hemorrhage, or cystic degeneration.[10] The GISTs are slow-growing tumors and have a prolonged survival period that's why imaging has great importance, not only for diagnosis but also to see the response of treatment. Various imaging techniques are available for the detection of GISTs including fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET), magnetic resonance imaging (MRI), and ultrasonography (US) but the imaging modality of choice is Computed Tomography (CT). Although FDG PET is most sensitive for the detection of GISTs, however, it is not easily available everywhere. [11, 12]

The differential diagnosis for esophageal GISTs on imaging depends upon the location and size. Smaller tumor limited to the wall of the esophagus most likely represents leiomyomas with differentials of duplication cyst, GIST, lipoma, and hemangioma. The endoluminal ultrasonography (EUS) with tissue biopsy is useful for histopathological diagnosis and further management of esophageal lesions.[11]

As esophageal gastrointestinal stromal tumors are very rare that is why there is a lack of clear recommendations regarding their surgical management. The surgical options range from the highly invasive esophagectomy to the much less invasive surgical tumor enucleation. Due to anatomical peculiarity of the esophagus, segmental-wedge resections are not usually performed.

Preoperatively it is difficult to categorize an esophageal tumor into benign or malignant by imaging examinations, like endoscopic ultrasound (EUS), computed tomography (CT), magnetic resonance imaging (MRI) andFluorodeoxyglucose positron emission tomography (FDG-PET). [18] Endoscopic or image-guided biopsy provides important information preoperatively and helps in surgical planning, but biopsy is considered a controversial technique due to the risk of tumor rupture and seeding. The difficulty in preoperative diagnosis makes it difficult for surgeons to select the surgical method. Imatinib, a tyrosine kinase inhibitor (TKI), has been shown to be highly effective in metastatic and neoadjuvant therapy. However, due to the rarity of esophageal GISTs, there is limited literature available regarding the neoadjuvant administration of Imatinib in patients with esophageal GISTs.[4] The aim of Imatinib therapy is downsizing the GIST to reduce the extent of resection and reduce the risk of intraoperative complications, including tumor rupture and reduce the chances of recurrence.

CONCLUSION

Esophageal gastrointestinal tumors are rare. Endoscopic or image-guided biopsy gives a definite diagnosis, but there is a risk of tumor rupture or tumor dissemination. Surgical resection is the only curative treatment for localized GISTs with the use of imatinib preoperatively and postoperatively. In addition to the most common imaging appearance of GIST as a solid tumor, it can also present as a cystic lesion and needs to be considered in the differential diagnosis of cystic esophageal lesions.

Figure.1 CT scan non enhanced

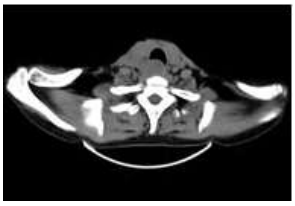


Figure.2 CT scan contrast enhanced

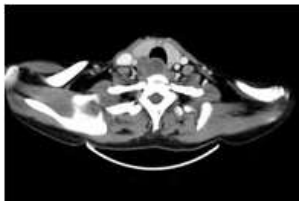


Figure.3 MRI T1W

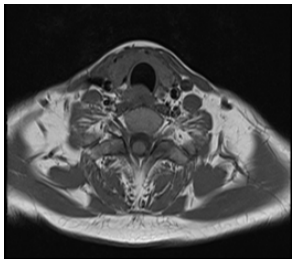
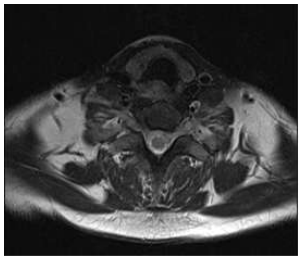


Figure.4 MRI T2W



Authors Contribution:
Junaid Iqbal: Conception
Sadia Rashid: Design
Hina Pathan: Analysis
Sorath Murtaza: Data interpretation

REFERENCES

1. A.B. Shinagare, K.A. Zukotynski, K.M. Krajewski, J.P. Jagannathan,J. Butrynski,J.L. Hornick, N.H. Ramaiya. Esophageal gastrointestinal stromal tumor: report of 7 patients. Cancer Imaging. 2012; 12(1): 100–108. Published online 2012 Apr 27. DOI: https://doi.org/10.1102/1470-7330.2012.0017
2. Wong C-S, Chu Y-CT, Khong P-L. Unusual features of gastrointestinal stromal tumor on PET/CT and CT imaging. ClinNucl Med. 2011;36:e1–e7. DOI: https://doi. org/10.1097/RLU.0b013e31820aa233
3. Hidalgo SJM, Martinez MD, Payan RM, et al. Gastrointestinal stromal tumors: A multidisciplinary challenge. World J Gastroenterol. 2018; 24(18): 1925–1941. DOI: https://doi.org/10.3748/wjg.v24.i18.1925.
4. Hihara J, Mukaida H, Hirabayashi N. Gastrointestinal stromal tumor of the esophagus: current issues of diagnosis, surgery and drug therapy. Transl Gastroenterol Hepatol. 2018; 3: 6. DOI: https://doi.org/10.21037/tgh.2018.01.06.

5. SmitiSripathi, KV Rajagopal, Rajendra Kumar Srivastava, and Anurag Ayachit. CT features, mimics and atypical presentations of gastrointestinal stromal tumor (GIST). Indian J Radiol Imaging. 2011 21(3): 176–181. DOI: https://doi.org /10.4103/0971-3026.85364

6. Zhang FB, Shi HC, Shu YS, Shi WP, Lu SC, Zhang XY, TuSS.Diagnosis and surgical treatment of esophageal gastrointestinal stromal tumors.World J Gastroenterol. 2015; 21(18): 5630–5634. DOI: https://doi.org/ 10.3748/wjg. v21.i18 .5630

7. Parab TM, DeRogatis MJ, Boaz AM, et al. Gastrointestinal stromal tumors: a comprehensive review. J Gastrointest Oncol. 2019; 10(1): 144–154. DOI: https://doi.org/ 10.21037/jgo. 2018.08.20.

8. Mushtaq S,Mamoon N,Hassan U, Iqbal M,Khadim MT,Sarfraz T. Gastrointestinal Stromal Tumors—A Morphological and Immunohistochemical Study. Journal of Gastrointestinal Cancer. December 2009, 40:109. DOI: https://doi.org/ 10.1007 /s12029-009-9108-5

9. DemetriGD, Benjamin R, Blanke CD, et al. NCCN task force report: optimal management of patients with gastrointestinal stromal tumors (GIST)—expansion and update of NCCN clinical practice guidelines. J Natl Compr Cancer Netw 2004;2:S1–S26.

10. BurkillGJ, Badran M, Al-Muderis O, et al. Malignant gastrointestinal stromal tumor: distribution, imaging features, and pattern of metastatic spread. Radiology2003;226:527–532. DOI: https://doi.org/10.1148/radiol.2262011880

11. JagerPL, Gietema JA, van der Graaf WT. Ima-tinibmesylate for the treatment of gastrointestinal stromal tumours: best monitored with FDG PET. Nucl Med Commun 2004;25: 433–438. DOI: https://doi.org/ 10.1097/00006231-200405000-00002

12. ChoiH, Charnsangavej C, de Castro Faria S, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinibmesylate treatment: a quantitative analysis correlated with FDG PET findings. AJR Am J Roentgenol 2004;183: 1619–1628. DOI: https://doi.org/10.2214 /ajr. 183.6.01831619

13. Shen EF, Arnott ID, Plevris J, Penman ID. Endoscopic ultrasonography in the diagnosis and management of suspected upper gastrointestinal submucosal tumours. Br J Surg 2002; 89:231-235. DOI: https://doi.org/10.1046/j.1365-2168.2002.02002.x

Case Report **Open Access**

Proliferative Verrucous Leukoplakia with Dysplastic Changes

Sanaa Ahmed, Muhammad Nasir, M. Sibghatullah Khan, Maria Naz, Uzma Bukhari

ABSTRACT:

Proliferative verrucous leukoplakia is one of the rare premalignant white lesions with highest conversion rate to malignancy. It grows gradually and irreversibly with multifocal presentation, exophytic and verrucous appearance. This lesion has been reported resistant to all therapeutic approaches including both non-surgical and surgical. Predisposing factors include female gender in the 6th decade of life. Proliferative verrucous leukoplakia has the highest tendency to neoplastic transformation and progression to oral squamous cell carcinoma and oral verrucous carcinoma in majority of the cases. The case of proliferative verrucous lesion clinically appearing benign presented here but on histopathology proven dysplasia in a patient with the history of smoking which he stopped six years back.

How to cite this Article:
Ahmed S, Nasir M, Khan MS, Naz M, Bukhari U. Proliferative Verrucous Leukoplakia with Dysplastic Changes. J Bahria Uni Med Dental Coll. 2022; 11(3): 172-174 DOI: https://doi.org/ 10.51985/JBUMDC202238

INTRODUCTION:

Proliferative Verrucous Leukoplakia (PVL) was categorized by the World Health Organization as "aggressive and distinct form of Oral Potentially Malignant Disorder (OPMD)" in the year 2005, with unknown etiology. OPMD are a group of conditions that are defined as "clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in a clinically normal mucosa". PVL grows gradually, persistently, and irreversibly, and it is mainly characterized by multifocal presentation, exophytic and verrucous appearance[1]. It is resistant to surgical and non-surgical approaches alike with highest recurrence and neoplastic conversion rate. It transforms to oral Squamous Cell Carcinoma (SCC) and oral Verrucous Carcinoma (VC)[1-3]. It has the highest malignant transformation rate among the other white lesions that is 47.7% [4]. While the chances to progress into oral squamous cell carcinoma is 70-100% [5]. Its diagnosis is based on the association of clinical and histopathological aspects.

In this case report, clinical case of Proliferative Verrucous Leukoplakia-PVL, which has been transformed to oral Verrucous Carcinoma were discussed. The literature revealed that it is included in the Oral Potentially Malignant Disorders, considering the neoplastic transformation of Proliferative Verrucous Leukoplakia to Verrucous Carcinoma. Moreover, it was suggested the National Institute for Health and Care Excellence (NICE) to make modifications in its head and neck cancer guidelines. It is recommended that Pakistan Association of Oral and Maxillofacial Surgeons (PAOMS) to make specific guidelines for the diagnosis of OPMD especially PVL.

Sanaa Ahmed
Assistant Professor, Department of Oral Medicine/Surgery
Jinnah Sindh Medical University
Email: drsanaaumair@gmail.com

Muhammad Nasir
House Officer, Dentistry
Jinnah Sindh Medical University
Email: drmuhammadnasir3@gmail.com

M. Sibghatullah Khan
Assistant Professor, Department of Oral Medicine/Surgery
Jinnah Sindh Medical University
Email: sibghat.khan@jcmu.edu.pk

Maria Naz
Lecturer, Department of Oral Medicine/Surgery
Jinnah Sindh Medical University
Email: maria.naz@jsmu.edu.pk

Uzma Bukhari
Professor, Department of Pathology
Dow University of Health Sciences,
Email: uzma.bukhari@duhs.edu.pk

Received: 16-Mar-2022
Accepted: 09-Jun-2022

CASE REPORT:

A 49-years married male patient presented to the oral medicine/diagnosis department of Sindh Institute of Oral Health Sciences, Karachi Pakistan, with the complaint of dental pain. During the clinical examination, a white lesion on the left buccal cheek mucosa was accidentally found. Lesion had thick, nodular, exophytic, verrucous surface 2 to 3 cm in size extending from oral commissure to the posterior part of the buccal mucosa. The lesion was slowly progressing over 6 years span with no sudden change during the past years [Figure 1]. Upon probing of any complain related to the lesion, the patient disclosed that he sometimes burning sensation was felt on the same side of the buccal mucosa. No other complaint of pus or blood discharge related to the lesion. The patient also gave history of similar lesion on right side of the buccal mucosa, which was surgically removed 7 years back, the lesion was biopsy proven leukoplakia. There was no cervical lymphadenopathy. Other findings included poor oral hygiene with heavy extrinsic staining of tobacco.

The patient had a history of smoking for 20 years with the consumption of 4 to 5 cigarettes per day and chewing tobacco in the past which he discontinued in 2008. He complained of insomnia with no known co-morbid and has been taking diazepam drug orally to treat insomnia.

Biopsy of the lesion under local anesthesia was performed and sent for histopathological analysis as these lesions has highest rate of conversion to neoplasia. Figure 2 shows the macroscopic features of biopsy comprised of single pale white, irregular, partially mucosa covered piece of tissue measuring 1x1x0.9cm and mucosa measuring 1x1 cm. Microscopic examination of the lesion revealed multiple fragments of squamous mucosa shows papillomatosis, hyperkeratosis with focal elongation of rete-ridges. At places dysplastic changes are seen. Cells show mild dysplasia, dyskeratotic squamous cells are present [Figure 3]. Special stains for fungus (PAS+/-D) highlights fungal hyphae and spores. The immunohistochemical stain CK5/6 highlights intact mucosal lining. A final diagnosis of Oral Verrucous Carcinoma was established [Figure 4]. The patient is then referred to affiliated hospital for surgical excision in the department of Oral and maxillofacial surgery.

Figure 1 Clinical picture of the lesion

Figure 2 Macroscopic features of biopsy

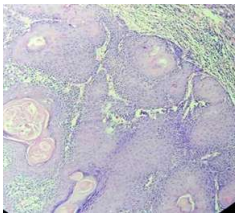


Figure 3 Histopathological picture showing dysplastic changes

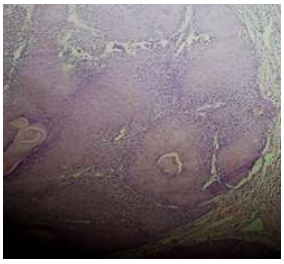
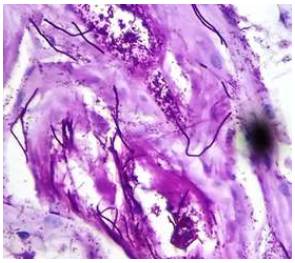


Figure 4 Fungal hyphae in the lesion.



DISCUSSION:

Proliferative Verrucous leukoplakia is a rare pathological lesion. It is common in females of 60 years or more in age with no alcohol or smoking habit [6]. The lesion commonly affects gingiva, buccal mucosa and alveolar ridge while tongue is rarely involved[7]. This case differs not only in gender as well as age predilection for the lesion. The lesion showed dysplastic changes over the period of 6 years with no clinically evident features of malignancy. These changes include no sudden increase in size, no presence of ulceration/red lesion and no lymph node enlargement. In the absence of habit, dysplastic conversion of the lesion is an alarming sign. Hence, long term follow-up of these lesions is very important. Diagnosis is on basis of the modified Carrard criteria[7]. Table 1 compares the reported cases of proliferative verrucous leukoplakia in the past decade. It shows the variation of the lesion not only in demographics but also in location and histopathological characteristics. Because the stages of progression of different sites in multifocal lesions are not always the same, patients should be continuously watched, with regular and repeating biopsies taken whenever there are changes in color, appearance, or size, as well as when new lesions appear. Patients with a whitish innocuous look and recurrence occurrences should be checked every six months as well. PVL can advance to VC or OSCC over time despite repeated treatment interventions, implying that PVL is linked to diffuse submicroscopic alterations in the oral mucosa, also known as "field cancerization" [7].

Literature review also supports that it is an aggressive premalignant lesion. various studies have reported that initial diagnosis varied from dysplasia to carcinoma in-situ to Squamous Cell Carcinoma [1, 5-6]. Recurrence rate is very high

Table 1 Summary of Case reports published on Verrucous Leukoplakia

Year of Publication	Demographics	Location	Histopathological feature
2011[6]	52 yrs Female	Right buccal mucosa + Palate	Verrucous leukoplakia with mild to moderate dysplasia
2017[8]	30 yrs Male	Left Lingual Margin	Verrucous hyperplasia with mild to moderate dysplasia
2019[9]	36 yrs Female	Gingiva	Early stage of PVL
2020[1]	75 yrs Female	Multiple proliferative lesions	Hyperkeratosis and mild epithelial changes
2020[10]	65 yrs Male	Right Buccal Mucosa	Mucosal stratified epithelium showing corrugated overgrowths with squamous epithelium which is hyperkeratotic and acanthotic.

in these lesions irrespective of the treatment option utilized alone or in combination. Most used option is surgery and laser ablation [7]. Recurrence can be at the same site or some other region in the oral cavity. Extensive resection is only suggested in cases with histopathological proven oral squamous cell carcinoma with bone invasion [7]. It was aimed to support the evidence that proliferative verrucous leukoplakia is an aggressive white lesion and should be treated as such, as well as it should be put in the list of alarming lesions as described in NICE guidelines 2015 on "Suspected cancer: Recognition and referral" as below [11]:

1. "A lump on the lip or in the oral cavity consistent with oral cancer."
2. "A red or red and white patch in the oral cavity consistent with Erythroplakia or erythro-leukoplakia."

It was recommended to highlight this pathology in local association of PAOMS to put forward evidence-based guidelines on early recognition of these lesions and referral by general dentist to minimize the risk of malignant transformation and mortality. Longitudinal studies are suggested to find out the factors that affect its conversion to Oral squamous cell carcinoma and the prevalence of these lesions among the white lesions in our population.

CONCLUSION:

Proliferative verrucous lesions have a high conversion rate to malignancy as well as high recurrence rate. Early diagnosis and 6 monthly follow up of benign lesions could decrease the morbidity associated with them.

Authors Contribution:
Sanaa Ahmed: Idea, Data curation, writing of final manuscript
Muhammad Nasir: Data Curation, writing of initial draft
Sibghat Ullah Khan: writing of Initial Draft
Maria Naz Shaheen: Data curation and Visualization
Uzma Bukhari: Writing of histopathological part of the case presentation and its interpretation

REFERENCES:

1. Figueroa L, Tortone M, Gilligan G, Pánico R. Protocolo de follow-up en'" leucoplasia proliferativa multifocal para evitar progresión maligna. Presentación de un caso clínico. Odontoestomatología. 2020;22(36):94-102 DOI: http://dx.doi.org/10.22592/ode2020n36a11
2. Bagan J, Scully C, Jimenez Y, Martorell M. Proliferative verrucous leukoplakia: a concise update. Oral diseases. 2010; 16(4):328-32 DOI: https://doi.org/10.1111/j.1601-0825 .2009.01632.x
3. Cabay RJ, Morton Jr TH, Epstein JB. Proliferative verrucous leukoplakia and its progression to oral carcinoma: a review of the literature. Journal of oral pathology & medicine. 2007 May;36(5):255-61 DOI: https://doi.org/10.1111/j.1600-0714.2007.00506.x
4. Pentenero M, Meleti M, Vescovi P, Gandolfo S. Oral proliferative verrucous leucoplakia: are there particular features for such an ambiguous entity? A systematic review. British Journal of Dermatology. 2014;170(5):1039-47 DOI: https:// doi.org/ 10.1111 /bjd.12853
5. Li, CC., Almazrooa, S., Carvo, I. et al. Architectural Alterations in Oral Epithelial Dysplasia are Similar in Unifocal and Proliferative Leukoplakia. Head and Neck Pathol 15, 443–460 (2021) DOI: https://doi.org/10.1007/s12105-020-01216-1
6. Ge L, Wu Y, Wu L-y, Zhang L, Xie B, Zeng X, et al. Case report of rapidly progressive proliferative verrucous leukoplakia and a proposal for aetiology in mainland China. World journal of surgical oncology. 2011;9(1):1-4 DOI: https://doi.org/10. 1186/1477-7819-9-26
7. Capella DL, Gonçalves JM, Abrantes AAA, Grando LJ, Daniel FI. Proliferative verrucous leukoplakia: diagnosis, management and current advances. Brazilian journal of otorhinolaryngology. 2017;83:585-93. DOI: https://doi.org/10. 1016/j.bjorl. 2016.12. 005
8. Shen J, Zhang Z, Jiang X, Guo W, Yang S. An unusual case report of an early proliferative verrucous leukoplakia. International journal of clinical and experimental pathology. 2017;10(11):11276.PMID: 31966481; PMCID: PMC6965850.
9. Leuke Bandara D, Jayasooriya PR, Jayasinghe RD. Proliferative Verrucous Leukoplakia of the Gingiva: An Early Lesion Refractory to Surgical Excision. Case reports in dentistry. 2019;2019. DOI: https://doi.org/10.1155/2019 /5785060
10. Fawzy MM, Nofal A, El-Hawary EE. Proliferative verrucous leukoplakia. Indian Journal of Dermatology, Venereology and Leprology. 2021;87(3):455. Doi: 10.25259/IJDVL_992_20.
11. Excellence NIfHaC. Suspected cancer: recognition and referral2015.Website:https://www.dental-referrals.org/wp-content/uploads/2015/09/NG12-Guidance-20150724.pdf

Case Report

Open Access

Cesarean Scar Pregnancy: Report of Two Cases

Habiba Sharaf Ali

ABSTRACT

Cesarean section scar ectopic pregnancy is rare pregnancy complication. They have become common due to an increase in cesarean sections worldwide. The following report outlines two cases of scar pregnancy in women; both women had a history of two previous cesarean sections. Both were type 2 scar pregnancies as they protruded from the uterine myometrium towards the uterine serosa.[1] The first woman initially received suction evacuation. The products, however, could not be entirely evacuated. As a result, laparotomy was performed. The second patient also underwent laparotomy due to her symptoms. Obstetricians need to keep a high index of suspicion while managing women with risk factors for an ectopic scar pregnancy. Failure to detect and pledge rapid treatment can lead to uterine rupture, massive hemorrhage, and maternal death. In the following report, presentations, and management of these two cases are discussed followed by a review of published literature.

Keywords: Cesarean scar pregnancy, suction curettage, laparotomy

How to cite this Article:
Ali HS. Cesarean Scar Pregnancy: Report of Two Cases. J Bahria Uni Med Dental Coll. 2022; 11(3):175-177 DOI: https://doi.org/ 10.51985/JBUMDC2021123

INTRODUCTION:

Cesarean scar pregnancy (CSP) or cesarean scar ectopic pregnancy is the embedding of a gestational sac in the uterine scar which has formed because of a previous cesarean section, previous myomectomy, uterine evacuation, or history of previous abnormally adherent placentation, manual removal of placenta, hysteroscopy, and in vitro fertilization.[2] It is a rare type of ectopic pregnancy reported to occur in approximately 1 in 2000 pregnancies.[3]

The risk of pathologically adherent placenta such as accretes increata, percreta, and scar pregnancy increases with the number of cesarean sections.[4] The symptoms of scar pregnancy vary; either the woman is asymptomatic or comes with lower abdominal pain and vaginal bleeding. The diagnosis is usually confirmed by a Transvaginal scan which shows an empty uterus with the presence of a gestational sac at the previous scar site as well as thin myometrium. Doppler ultrasound is also helpful as it shows quantifiable vascularization around the cesarean section scar.[5] Magnetic resonance imaging (MRI) is an additional tool used for CSP.[6] The best possible management of the patient with a sonographic diagnosis of suspected CSP remains uncertain and challenging. Some conservative treatment modalities are curettage, hysteroscopy, local or systemic methotrexate alone, or removal of trophoblastic tissues via laparotomy or laparoscopy, and uterine artery embolization.[7]

Habiba Sharaf Ali
Professor/consultant, Department of Obstetrics/Gynecology
Ziauddin university/Kharader General Hospital
Email: rabel5@yahoo.com

Received: 21-Dec-2021
Accepted: 31-May-2022

Almost all pregnancies diagnosed as CSP are terminated. If they are left to continue, they can result in catastrophic complications such as uterine rupture, hemorrhage, a high risk of hysterectomy causing severe maternal mortality and morbidity, and future fertility concerns.

CASE REPORTS:

Two cesarean section scar pregnancy cases were confirmed and treated in the Obstetrics and the Gynecology Department of Kharadar General Hospital, Karachi. The cases were reported in two months, from May to June 2021, at 7 to 8 weeks gestation. The details were as follows- In both cases, diagnosis was based on the presence of an empty uterus and cervical canal. The gestational sac was located anteriorly with a diminished myometrium layer between the bladder and the sac.

Case 1: A 35-year-old female, with a history of two previous cesarean sections came with complaints of two months of amenorrhea and vaginal bleeding. An initial ultrasound scan confirmed an irregular sac in the lower uterine segment measuring 1.9x1.4 cm. Endometrial thickness was 0.6cm with hyper vascular trophoblastic tissues around the sac on Doppler suggesting missed scar pregnancy. Her early beta HCG was 844. Primarily the patient was managed by suction curettage under general anesthesia. On examination, during the procedure cervical os was open. The uterus was bulky and empty. Few pieces mixed with clots were removed from the scar area. Suddenly the patient started bleeding profusely per vaginally so the procedure was stopped and uterine packing was done which controlled the bleeding. Two days later, her beta HCG was 760 raising high suspicion of retained products. An ultrasound scan done showed an endometrial thickness of 0.6cm. The irregular cystic structure

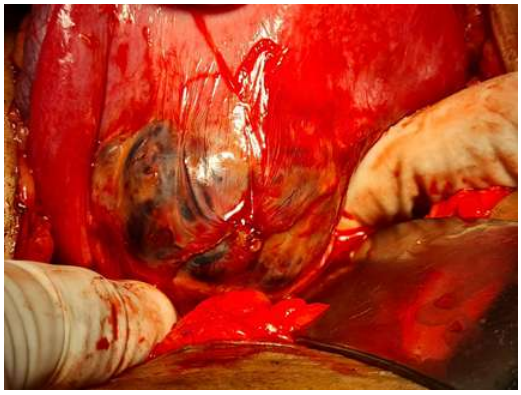
was seen in the scar region's lower segment of the uterus, measuring 1.3x0.6 cm. It may be collapsed gestational sac with thick trophoblastic tissue with increased vascularity. The patient constantly had pain and bleeding. Laparotomy was undertaken. On opening, the peritoneal cavity bladder was seen adherent to the uterine scar. The previous scar was seen to be covered with a cystic structure with an area of hemorrhage and necrosis. There were no myometrial tissues. Figure 1 shows the lower uterine segment with absent myometrium and visible sac. The trophoblastic tissues were removed and the uterus was stitched in two layers. The patient made an uneventful recovery. The histology confirmed the retained products of conception.

Figure 1: Case 1 Lower Uterine Segment With Absent Myometrium and Visible Sac

Case 2: A 22-year-old female with history of previous cesarean section came to the gynecology outpatient department with the complaints of two months of amenorrhea and slight bleeding per vaginum. The abdomen was soft and not tender, per vaginal examination revealed close cervical os. Transvaginal ultrasound revealed irregular sacs seen in the lower segment of the uterus in the scar region in the lower myometrium traversing the full length of the anterior myometrium and protruding the serosal layer. It measures 1.9 x1.4 cm with trophoblastic tissue around it with evidence of circulation and hypervascularity. On Doppler scan findings were suggestive of missed scar pregnancy. Her serum beta HCG was around 25000mIU/ml. The repeat Beta HCG was 19000. She lost to follow up for two weeks and then came in an emergency with complaints of severe lower abdominal pain. Ultrasound done in emergency showed the same findings as before. Due to her symptoms and our earlier experience with the first case we decided to take the patient to theatre for laparotomy.

On opening the peritoneal cavity the bladder was seen adherent to the lower uterine segment covering the scar area. In the lower uterine segment, a bulging gestational sac was seen covered by the serosal layer. There was no myometrium, small nick was given and the whole sac with the placenta came out. Figure 2 shows bulging gestational sac with absent myometrium. Through the gap in the lower uterine segment, the uterus was explored by fingers to look for any remaining trophoblastic tissues. The incision was closed in two layers. The estimated blood loss was minimal as there was no bleeding from the scar site.

Figure 2 Case 2 Bulging Gestational Sac with Absent Myometrium



DISCUSSION:

There is a recent rise in scar pregnancy due to increased cesarean rate and early diagnosis. The diagnosis of choice is ultrasound scan and preferably Doppler scan. Both our patients were diagnosed by Transvaginal ultrasound.

The best possible and optimal management of CSP is unclear and a variety of therapeutic strategies are being used and so far no definitive and universal treatment is available. Initially, the first-line approach considered by "The Practice Committee of the American Society for Reproductive Medicine"[8] was systemic methotrexate but the systemic review published by Kanat-Pekt showed that systemic methotrexate was successful in 8.7 % of cases.[9] In the same review hysterectomy by laparoscopy or laparotomy produced the same results and was successful in 92% of cases. He recommended both methods to be safe and efficient and should be adopted as primary treatment modalities for CSP. He also noted that D&C as a first approach is associated with hemorrhage as in our case, infertility poor obstetric outcome.

In a study done by Timor-Tritsch IE and colleagues, 26 stable patients between gestational age of 6 to 14 weeks were included, where combined intramuscular and intra gestational MTX injection were used.[4] They reported no complications. Ayºe Karahasanoglu, MD in their study successfully used suction curettage under ultrasound guidance and balloon tamponade as the main on 13 patients.[10] Both of our scar pregnancies were type 2 and they have a threatening prognosis due to chances of spontaneous uterine rupture, hemorrhage and maternal death so termination of pregnancy was decided by doing laparotomy. Termination of pregnancy is recommended as leaving the pregnancy

results in placenta previa, accreta, uterine rupture, and related life-threatening massive hemorrhage.[11] In a recently published case report patient with a cesarean scar, pregnancy was ultimately managed by doing a partial hysterectomy due to excessive hemorrhage. Initially methotrexate, D &C, and Baku balloon were tried.[12]

Our first patient underwent suction curettage initially but during the procedure, she started bleeding per vaginum and uterine packing was done to control the hemorrhage. She could have been managed laparoscopically but due to the unavailability of expertise and the acute situation, laparotomy was performed. This is small case series of two patients only. It's our first experience managing CSSP. Due to the condition of the patients we were unable to try any other options.

CONCLUSION:

We report two cases of cesarean scar pregnancy. We found that the treatment of patients with cesarean scar pregnancies is a challenge. We conclude that treating patients of Cesarean scar pregnancy with definite treatment such as by hysteroscopy, laparoscope, or by doing open surgery avoids the need for further interventions, blood loss, issues of the retained product of conceptions, and fertility issues.

Authors Contribution:
Habiba Sharaf Ali: Main idea, manuscript writing, research, proof reading

REFERENCES:

1- Majangara et al. Cesarean section scar ectopic pregnancy - a management conundrum: a case report journal of Medical Case Reports 2019; 13:137.

2- Patel MA. Scar ectopic pregnancy. J Obstet Gynaecol India. 2015; 65(6):372–5. DOI: 10.1007/s13224-015-0817-3.

3- Jayaram PM, Okunoye GO, Konje J. Caesarean scar ectopic pregnancy: diagnostic challenges and management options. Obstet Gynaecol. 2017. https://doi.org/10.1111/tog.12355

4- Timor-Tritsch IE, Monteagudo A, Santos R, et al. The diagnosis, treatment, and follow-up of cesarean scar pregnancy. Am J Obstet Gynecol 2012; 207:44.e1-13. DOI: 0.1016/j.ajog.2012.04.018.

5- Piotr Pêdraszewski, Edyta WlaŸlak, Wojciech Panek, Grzegorz Surkont J Ultrason 2018; 18: 56–62. doi: 10.15557/ JoU. 2018. 0009

6- Chiang AJ, La V, Chou CP, Wang PH, Yu KJ: Ectopic pregnancy in a cesarean section scar. Fertil Steril 2011; 95: 2388–2389. DOI: 10.1016/j.fertnstert.2011.03.104.

7- Birch Petersen K, Hoffmann E, Rifbjerg Larsen C, Svarre Nielsen H: Cesarean scar pregnancy: a systematic review of treatment studies.Fertil Steril 2016; 105: 958–967. DOI: 10.1016/j.fertnstert.2015.12.130.

8- The Practice Committee of the American Society for Reproductive Medicine Medical treatment of ectopic pregnancy: a committee opinion. Fertil Steril. 2013; 100(3):638-44.DOI: 10.1016/j.fertnstert.2013.06.013.

9- M. Kanat-Pektas et al. Systematic review: What is the best first-line approach for cesarean section ectopic pregnancy? Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 261-269. DOI: 10.1016/j.tjog.2015.03.009.

10- Ayºe Karahasanoglu, MD, Successful Treatment of Cesarean Scar Pregnancy with Suction Curettage: Our Experiences in Early Pregnancy. Ochsner Journal 2018; 18:222–225. DOI: 10.31486/toj.17.0118.

11- Ash A, Smith A, Maxwell D. Caesarean scar pregnancy. BJOG 2007; 114:253–263. .

12- Asma Kashif .Scar Ectopic Pregnancy. Journal of the College of Physicians and Surgeons Pakistan 2020; 30(08): 884-885.

Letter to Editor **Open Access**

Monkeypox: An Ignored Adversary

Sadaf Haris

How to cite this Article:
Haris S, Monkeypox: An Ignored Adversary J Bahria Uni Med Dental Coll. 2022;12(3):178 DOI: https://doi.org/ 10.51985/ JBUMDC202290

Dear Editor,

Monkeypox was first discovered in monkeys in 1958, so it was named after that. The first case was seen in humans in 1970. Monkeypox virus is the causative agent, the same family as smallpox, but causes a less severe disease.ÊThe Congo Basin and West African strain are the two types of strains. All cases identified in the outbreak have been caused by the West African strain.[1]

The mode of transmission of Monkeypox virus is via intimate contact with sores, biofluids, aerosols, and contaminated fomites. The latent period lasts between 6 and 13 days but may vary from 5 to 21 days. Monkeypox is usually self-resolving but may become severe in youngsters, expectant women, and immunocompromised personnel.[2]

According to the World Health Organization (WHO), there are 12 endemic countries where the monkeypox virus prevails.[3] However, in the past few weeks, 12 non-endemic WHO member states have reported newfound cases of the monkeypox virus. Although no deaths have been reported in recently identified cases, The United Kingdom has surpassed this list with the highest number of confirmed cases reported between 13 and May 21, 2022. [3] Based on current data, cases have been identified mostly in homosexuals pursuing care in sexual and general care clinics.

The disease had not received any regard when it was an issue of the African region, but as soon as estimable countries started having a rise in cases, it came to immediate attention worldwide. For decades, the monkeypox virus had cohabited with African populations. With increasing urbanization, relocation, and friction; wildlife and human contact is becoming more common, and such contiguity will advocate congestion of zoonotic bugs. At present, we are lacking in knowledge of microorganisms that might surface, so, we need an adequate investment in vigilance.

Since the emergence of the monkeypox virus in non-endemic countries, national and provincial health authorities in Pakistan were put on high alert on May 23, 2022, as per the notification from the National Institute of Health (NIH) which emphasized that the virus could also outbreak in Pakistan. Even though Pakistan hasn't reported its first confirmed case of monkeypox yet, the spread of the virus to the country is almost inevitable. Pakistan has a massive number of flights coming from the regions where monkeypox is on rise, screening for the virus should be mandated at the airports, and suspected or confirmed cases must be quarantined for a prodromal period. The struggling health care system will be on the verge of collapse if monkeypox starts to spread. Pakistan does not have any diagnostic facility for the virus, the health department has declared samples can be sent abroad for testing in case of emergencies which further threatens the spread. [4] Therefore, to avoid a monkeypox/COVID-like outbreak in Pakistan, relevant health authorities must employ a proactive approach and initiate nationwide awareness campaigns that emphasize the importance of effective hygiene practices, self-quarantining, and other relevant safety protocols.

To date, the strategy to restrain monkeypox eruption depends on mass education and timely detection of cases to decrease the virus transmission. Hugh Adler and colleagues[5] have mentioned in one of their studies that some trials are being conducted to see the efficacy of antivirals in controlling monkeypox. A study is ongoing in Congo exploring the role of smallpox vaccination, and another study will monitor the role of antiviral tecovirimat in Africa.[6] Meanwhile, African doctors vast experience for the treatment of Monkeypox should be acknowledged and their guidance should be taken for further evaluation and management of the disease.

Sadaf Haris
Assistant Professor, Department of Family Medicine
Bahria University Medical & Dental College, Karachi
Email: sadafharis16@gmail.com

Received: 23-Jun-2022
Accepted: 30-Jun-2022

Authors Contribution:
Sadaf Haris: Substantial contributions to the conception criticaly evaluation of intellectual content

REFERENCES

1. Paper, T., Editor, R., Page, O., 2022, B„ Quotes, S., Sports, O., gardens, H. and outbreak, P., 2022.ÊPaying a price: The Hindu Editorial on monkeypox outbreak in Europe. [Internet] Thehindu.com. [Cited 22 June 2022].Available at: https://www.thehindu.com/opinion/editorial/paying-a-price-the-hindu-editorial-on-monkeypox-outbreak-in-europe/article65473062.ece
2. Multi-country monkeypox outbreak in non-endemic countries [Internet]. Who.int. 2022 [cited 22 June 2022]. Available from:
3. Ola P. The origin of the mysterious multi-country monkeypox outbreak in non-endemic countries.
4. Geo News No Diagnostic Testing Facility [Internet]. 2022 [cited 27 June 2022]; Available from Monkeypox in Pakistan: Health Ministry (2022) https://www.geo.tv/latest/418686-no-diagnostic-testing-facility-available-for-monkeypox-in-pakistan-health-ministry
5. The Guardian view on monkeypox: communication is crucial | Editorial [Internet]. the Guardian. 2022 [cited 22 June 2022]. Available from: https://www.theguardian. com/commentisfree /2022/jun/05/the-guardian-view-on-monkeypox-communication-is-crucial
6. Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, et al. NHS England High Consequence Infectious Diseases (Airborne) Network. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis. 2022 May 24:S1473-3099(22)00228-6. DOI: https://doi.org/10.1016/S1473-3099(22)00228-6.

Instructions to Author

The Journal of Bahria University Medical and Dental College abbreviated as JBUMDC is a peer reviewed quarterly multidisciplinary biomedical journal of basic and clinical health sciences. It accepts manuscripts prepared in accordance with the "Uniform Requirements for Submission of Manuscripts for Biomedical Journals, updated December 2015", adopted by International Committee of Medical Journal Editors (ICMJE) & PMDC guidelines for Medical & Dental journals. The Journal will encompass manuscripts from all fields of biomedical sciences in the form of Editorial (Invited/Editor), Original Article, Review Article (narrative reviews and systematic reviews), short communication, Commentary, case study, and letter to editor.

Peer Review Policy:

Every paper will be read by the editor and then will be sent to two reviewers, one internal and one external reviewer. If statistical analysis is included assessment by statistician will be carried out.

Plagiarism:

JBUMDC follows the ICMJE, PMDC and HEC guidelines. Each manuscript will be scrutinized. Plagiarism of the manuscript should be less than 18%.

Preparation of Manuscript:

Type the manuscript on ISO A4 (212 × 297 mm), with margins of at least 25 mm (1 inch). Type or print on only one side of the paper. Use double spacing throughout the manuscript. Number pages consecutively, beginning with the title page. Put the page number in the lower right-hand corner of each page.

Contents of Manuscript for submission:

Submission items include a Covering letter, letter of undertaking duly signed by all authors, Ethical Review Committee (ERC) Letter, Author's declaration on JBUMDC template stating authors contribution, Title page and the Manuscript [Abstract, Key words, Introduction, Methodology, Results, Discussion, Conclusion, Acknowledgement, Authorship, Conflict of interest, References, Tables , Figures]**.** Title page should have complete title of the manuscript, along with the short running title, the names of all authors with qualifications, their department, affiliation, telephone number, e-mail, corresponding author, address for correspondence, short running title, source of funding (grant/equipment/drugs), number of figures and tables, total word count, total number of pages. Original manuscript should be of 2500 words excluding abstract and references and the references should be at least 20-25 for original study.

1. Abstract

It should have no more than 150 words for unstructured abstracts or 250 words for structured abstracts. The structured abstract should include:

1) Objective, 2) Study design and setting, 3) Methodology, 4) Result and 5) Conclusion.

[state the purpose of the study (objective), basic procedures (methodology with study design, subjects/animals, place & duration of study, drug/chemical/equipment, procedure or protocol), main findings (results) and conclusion (It should emphasize new and important aspects of the study.)]

Below the abstract provide, 3-10 key words that will assist indexers in cross-indexing the article. The key words should be in alphabetical order.

2. Introduction

State the purpose of the article and summarize the rationale for the study. Give only strictly pertinent references and do not include data or conclusions from the work being reported. At least 10 to 12 references should be included in the introduction. International and national literature review indicating the rational and objective of the study.

3. Methodology:

This section should include a statement indicating that the research was approved by independent local or regional or national review body(eg. Ethics committee, institutional review board) with ERC number. Clearly describe the type of study, selection of observational or experimental participants, including eligibility and exclusion criteria and a description of source population. Identify the age, gender and other characteristics of subjects. Mention the sample size and how it is calculated and the sample technique. Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. For randomized clinical trials provide information on all major study elements, including the protocol (study population, interventions or exposures, outcomes, and the rationale for statistical analysis), assignment of interventions (methods of randomization, concealment of allocation to treatment groups), and the method of masking (blinding). Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract. Describe statistical methods with enough detail to enable a knowledgeable person with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Define statistical terms, abbreviations, and most

symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

4. Results

Present your results in logical sequence in the text, tables, and illustrations according to the objective of the study. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. Describe appropriate indicators of measurement error or uncertainty such as confidence intervals, P values. Report complications of treatment and dropouts from a clinical trial. Specify any general-use computer programs employed for analysis.

5. Discussion and Conclusion

Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or other material given in the Introduction or the Results section. Include in the Discussion section the implications of the findings and their limitations, including implications for future research. Relate the observations to other relevant studies. Link the conclusions with the goals of the study.

6. Acknowledgment

List all contributors who do not meet the criteria for authorship, such as a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Financial and material support should also be acknowledged.

7. Authorship

Authorship credit is based only on the criteria laid down by International committee of Medical Journal Editors (http://www.icmje.org/recommendations/browse/roles-and-responsibilibies/defining-the-role-of-authore-and-contributors. html).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; and 3) final approval of the version to be published. 4) Agreement to be Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All Conditions must be met. Authors should provide a description of what each contributed.

8. Conflict of interest

All authors have to disclose and submit any financial /personnel relationship that might bias and inappropriately influence their work.

9. References

Minimum 50% of the references must be from last five years. Local references must also be included. Vancouver style should be followed. Examples are:

a) Standard journal article

List the first six authors followed by et al. Mention the DOI as follow in the end of reference .
I) Less than 6 authors:

Maqbool MS, Shahid A, Shafqat H. To Evaluate and Compare Clinical Effects of Varying Bolus Doses of Oxytocin in Patients Undergoing Caesarean Spinal Delivery.J Bahria Uni Med Dental Coll. 2020;10(4):261-265 DOI: https://doi.org/10.51985/JBUMDC2020018

II) More than six authors:

Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996;73:1006-12. DOI: https://doi.org/10.51985/JBUMDC2021022

b) Organization as author

The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164: 282-4

c) No author given

Cancer in South Africa [editorial]. S Afr Med J 1994;84:15

d) Chapter in a book

Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh

JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78

e) Newspaper

Hasan Mansoor. Excessive use of drugs creating resistance to antibiotics. The Dawn 2013, 24 June; sect. Metropolitan (col.1-4)

10. Tables

Type or print out each table with double spacing on a separate sheet of paper. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes. Explain in footnotes all nonstandard abbreviations that are used in each table. Identify statistical measures of variations, such as standard deviation and standard error of the mean. Do not use internal horizontal and vertical rules.

11. Illustrations (Figures)

Figures should be professionally drawn and photographed. Photographic prints 127 × 173 mm (5 × 7 inches). Photomicro-graphs should have internal scale markers. Symbols, arrows, or letters used in photomicro graphs should contrast with the background. If photographs of people are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.

Figures should be numbered consecutively according to the order in which they have been first cited in the text. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material.

Legends for Illustrations

Type or print out legends for illustrations using double spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.

Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units. Temperatures in degrees Celsius, Blood pressure in millimeters of mercury and all hematologic and clinical chemistry measurements in the metric system in terms of the International System of Units (SI).

Abbreviations and Symbols

Use only standard abbreviations. Avoid abbreviations in the title and abstract. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

Sending the Manuscript to the Journal

Submit manuscript by OJS: https://jbumdc.bahria. edu.pk/index.php/ojs

All correspondence regarding submitted manuscripts will be via e-mail.

S No	Type of Article	Abstract type and word count	Key words	Total word count	References	Tables (Max)	Figures (Max)
1	Editorial	-	-	1000-1500	10-12	-	-
2	Review Article	Unstructured (150)	3-6	3000-3500	40-60	4	2
3	Original Article	Structured (250)	3-10	2500-3000	20-25	3	2
4	Medical Education	1. Original Structured (250)	3-10	2500-3000	20-25	3	2
		2. Review Unstructured (150)	3-6	3000-3500	40-60	4	2
		3. Reproducible work (guide lines, questionnaire)	Mention Source, Accessed on, Retrieval date				
5	Short Communication /Commentary/ Opinions/ Perspective	-	-	1200-1500	15-20	2	1
6	Student Corner	1. Original article Structured (250)	3-10	2500-3000	20-30	4	3
		2. Views/Perspectives/ Opinions Unstructured (150)	3-6	1200-1500	8-10	1	1
7	Case Report	Unstructured (150)	3-5	1200-1300	10-12	1	5
8	Letter to Editor	-	-	400-500	1-5	-	-

JBUMDC
Journal of Bahria University Medical & Dental College
Peer Reviewed Multidisciplinary Quarterly Published Journal
ISSN (print): 2220-7562, ISSN (online): 2617-9482, CODEN: JBUMB7
Recognized by HEC
Online edition is available at URL: https://jbumdc.bahria.edu.pk,
Indexed with Index Medicus for the Eastern Mediterranean Region (IMEMR),
https://vlibrary.emro.who.int/journals/jbumdc-journal-of-bahria-university-medical-and-detal-college/
ROAD Directory of Open Access Scholarly Resources at https://portal.issn.org/resource/ISSN/2617-9482
Pakmedinet at www.pakmedinet.com/jbumdc,
Google Scholar at https://scholar.google.com.pk/,
Crossref at https://doi.org/10.51985/aluu2996
ICMJE at https://www.icmje.org/journals-following-the-icmje-recommendations/#J
Bahira University DSpace Repository at http://111.68.99.22:8080/xmlui/handle/123456789/6388,
Pakistan Scientific and Technological Information Center (PASTIC) at http://pastic.gov.pk/

Journal of Bahria University Medical & Dental College

Published by Bahria University Health Sciences Campus Karachi
Adjacent PNS SHIFA DHA Phase II Karachi, Pakistan
+92-21-35319491-9
http://jbumdc.bahria.edu.pk
editor.bumdc@bahria.edu.pk
https://www.facebook.com/jbumdc/, https://www.facebook.com/journal.bumdc.7