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Editorial

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Diagnostic Pathology in the Era of Precision Medicine

Summaya Shawanna, Yasmeen Taj

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The ever-increasing importance of targeted therapy in the management of cancerous and non-neoplastic diseases calls for novel, advanced techniques of diagnostic pathology. The past decade has witnessed substantial changes in how cancer patients are managed, with a pronounced focus on precision medicine based on genomic profiles and gene expression analysis, thus discarding the "one-size-fits-all" approach[1]. Understanding tumor development and acquiring information regarding the genetics, transcriptomics, proteomics, and epigenetics of pathological lesions, especially cancers, is central to precision medicine[2]. Several state-of-the-art techniques, especially those directed towards the molecular characterisation of diseases, have been developed to meet these challenges. Completing the Human Genome Project and the advent of pharmacogenomics, disease management has changed drastically, especially that of cancers. Oncology is now considered to be the first choice for targeted therapeutics. In cancer therapeutics, precision medicine aims to develop tailored therapies for patients according to the molecular pattern of the tumor.[3,4]

More recently, cancer researchers have focused on non-invasive methods for diagnosing molecular profiles of tumors. One such diagnostic tool, "liquid biopsy," relies on circulating tumor cells and cancer cell-derived circulating components like ctDNA and exosomes. These components are isolated from peripheral blood and can be utilized for genomic and proteomic diagnostic techniques.[5,6] Liquid biopsy is being recognized as an effective non-invasive, real-time approach for detecting biomarkers in body fluids for screening, diagnosing, and predicting various cancers. Potential clinical applications of liquid biopsy include genomic profiling of tumors, recognizing molecular targets for therapy, response to therapy, and assessing minimal residual disease.[7] Role of liquid biopsy in cancer screening is still undecided and is an open arena for future research.

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Advancement in molecular diagnostic techniques and data processing have made possible analysis of large amounts of data and has provided opportunities for suitable and effective interventions. Next-generation sequencing techniques have proved invaluable for gaining insights into tumor molecular profiles and the development of targeted therapies.[8] Sequencing and array technologies generate extensive data and make it possible to unravel the potential mechanism underlying the alteration in morphology and function of tumors. These techniques can identify multiple and epigenetic alterations including, insertions and deletions, copy number variation, chromosomal rearrangements, and single nucleotide mutations. These techniques can be applied to specific genes, entire protein-coding regions of DNA (whole-exome sequencing) or the entire genome (whole genome sequencing). The advent of computational biology and bioinformatics has made it possible to handle, store and analyse the extensive data generated by next-generation sequencing. Diagnosing cancers and predicting cancer behaviour and progression has become more precise owing to these advancements. Thus modern molecular techniques like NGS have become an inevitable tool in cancer diagnostics. The same results would be impossible with the conventional pathological diagnostic methods that rely on morphological changes and can predict only a general need for therapy. However, it will give little insight regarding the precise target therapy based on the underlying genetic alteration and its functional consequences.

Even though the genomic characterisation of tumors has been of immense value, DNA aberrations alone do not picture the related biological pathways. This gap has been very efficiently filled by transcriptomic studies that have emerged as essential techniques in molecular diagnostics.[9] Moreover, transcriptomic studies have paved the way for developing bioinformatics tools, improving the understanding of differential gene expression regarding biological functions.[10] RNA sequencing (RNA seq), a type of whole-genome transcriptomic technique, is utilized to characterize and quantify the entire RNA content in a cell or tissue. This technique has improved immensely since its early development, especially regarding data quality related to translated and non-translated RNA molecules and gene fusions.[11] RNA seq has also revolutionized differential expression analysis in specific cell types. More recently, single-cell RNA sequencing methods have been developed

that enable accurate gene expression profiling with a limited number of reads.[12] Targeted breast cancer therapeutics is one of the success stories in the achievements of transcriptomics in cancer management in the near past. Whole-genome sequencing has provided substantial knowledge of, breast "cancers' genomic profiles, including single nucleotide pleomorphism, copy number variations, and driver mutations.[13] One of the significant achievements in this regard is the advent of RNA sequencing, especially mRNA sequencing. This technique has been effectively utilized to characterise receptor-negative breast cancers (triple-negative breast cancers). It has been a valuable aid in evaluating differential gene expression between TNBCs and non-TNBCs hence characterisation of TNBCs and their subclassification.[14] This classification has opened avenues for developing precision medicine for triple-negative breast cancers with specific molecular subtypes, a ray of hope for patients with this aggressive tumor. siRNA screening has also uncovered genetic variants participating in cancer development and progression.[15] An increasing number of miRNAs (microRNAs) are being identified by transcriptomic studies, and many of these play critical roles as tumor suppressors and promoters.[16] MicroRNAs are often dysregulated in cancers, and profiling miRNAs has given insights into the complex mechanisms underlying oncogenesis. miRNA expression may be used to classify tumors and design effective therapies, and multiple clinical trials have shown promising outcomes.

While there has been a boom in developing new and more precise molecular diagnostic techniques worldwide, we lack behind with regards to utilizing these advancements to develop even a basic genetic profile of cancer patients in our population. There is an extreme shortage of knowledge regarding the mutational profiles of cancer patients in the Pakistani people. To develop targeted therapies directed at treating the prevalent cancers in our part of the world, it is imperative first to understand our genetically diverse population's genomic and expression profiles of our genetically diverse population. In the same regard, trained individuals in molecular pathology, molecular medicine, and bioinformatics are indispensable assets. Qualified individuals in molecular pathology, molecular medicine, and bioinformatics are essential assets, trained individuals in molecular pathology, molecular medicine, and bioinformatics. It is high time that we take advantage of the rapidly emerging advancing diagnostic techniques to identify the biological hotspots and networks in various prevalent cancers in our population for effective drug development and design.

Authors Contribution:
Summaya Shawanna: Idea Conception, writing
Yasmeen Taj: Literature Review

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Orginal Article

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Impact of Vitamin C as an Adjuvant Agent on Glycemic Indices in Type 2 Diabetes Mellitus: Randomized Clinical Trial

Shabzain Ishrat, Talea Hoor, Muhammad Sajid Abbas Jaffri, Shizma Junejo, Mehreen Lateef

ABSTRACT

Objectives: To evaluate the effects of adjuvant vitamin C therapy with oral hypoglycemic on FBS, RBS and HbA1c and to find out the correlation of Vitamin C with glycemic indices.

Study Design & Settings: This randomized open label clinical trial was conducted at Bahria University Medical & Dental College (BUMDC) in collaboration with NMC, Karachi from October 2018 to April 2019.

Methodology: A total of 160 known type -2 males and females, uncomplicated diabetics, aged 40-65 years with FBS= 200 mg/dl, HbA1c = 8.5% and diabetes duration > 5years were enrolled from diabetic clinic of NMC after written informed consent. They were divided into control group and treatment group by sealed envelope technique. Control group received oral hypoglycemic drugs while treatment group received vitamin C 500 mg per orally BD with oral hypoglycemic drugs with advice of diet control and daily exercise. Patients were subjected to FBS, RBS and HbA1c at baseline and at the end of 90 days. SPSS version 23.0 was used for data analysis. The results were expressed as mean ± standard deviation (SD). P value<0.05 was considered as statistically significant.

Results: In control group FBS and RBS reduced by1mg /dl and 7mg/dl from day-0 to 90. In treatment group FBS reduced by 14mg/dl and RBS reduced by 21mg/dl from day-0 to 90. HbA1c increased by 0.7% in control group and decreased by 0.4 % in treatment group at the end of 90 days. Negative correlation is observed between Vitamin C and glycemic indices.

Conclusion: Adjuvant vitamin C therapy with oral hypoglycemic drugs in type-2 diabetics reduced FBS, RBS and HbA1c and exhibited negative correlation with glycemic parameters.

Keywords: Correlation, Fasting blood sugar, HbA1c, Random blood sugar, Type 2 diabetes mellitus, Vitamin C.

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INTRODUCTION:

Diabetes mellitus (DM) is a metabolic disorder characterized by elevated levels of blood glucose. It is one of the oldest diseases known to mankind.[1] Type 2 DM is characterized by hyperglycemia, hyperlipidemia, insulin resistance etc; caused by gradual destruction of â cells.[2,3,4,5] It accounts for 90% to 95% of the diabetic patients.[6,7] International Diabetes Federation (IDF) has estimated that 1 in 11 adults were diagnosed with type 2 DM in 2015 and has predicted that there will be 642 million people with type 2 DM in 2045. The disease is more common in developing countries as compared to developed nations.[8] According to IDF, Pakistan has high prevalence of disease and is in the list of top ten countries with increased prevalence of type 2 DM. About 6.6 million people live with type 2 diabetes in Pakistan.[9] Pakistan is the sixth most populous country and the trend for urbanization has increased in the recent years. Sedentary lifestyle, increased consumption of high calorie diet, lack of exercise and stressful conditions has led to increased prevalence of disease in Pakistan.[10] Long standing hyperglycemia of type 2 diabetes mellitus leads to increase in oxidative stress by production of reactive oxygen species. These reactive oxygen species lead to progression of disease into complicated diabetes mellitus which includes micro-vascular and macro-vascular complications.[11] It has been reported by various studies that there is a strong association between oxidative damage and progression of disease. The imbalance between the rate of production of reactive oxygen species and to counteract them by antioxidants is the main

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factor behind continuous oxidative damage in type 2 DM.

Researches are being conducted globally to effectively control the glycemic indices so as to prevent and/or control the complications associated with type -2 diabetes and hence to reduce morbidity and mortality.[11] Co-administration of vitamin C along with drug treatment of type 2 diabetes mellitus might facilitate the control of glycemic indices. Therefore, present study was conducted to evaluate the effects of vitamin C on glycemic control in type 2 diabetes mellitus and to find out the correlation of vitamin C with the glycemic indices.

METHODOLOGY:

This randomized clinical trial was conducted from October 2018 to April 2019 after ethical approval numbered ERC 50/2018 from BUMDC and FRC in collaboration with diabetic clinic of National Medical Centre (NMC), Karachi. Patients with known history of diabetes without complications, aged 40 to 65 years, both male and female with FBS = 200 mg/dl, HbA1C = 8.5%, normal baseline investigations of LFTS, RFTS, diabetes duration > 5 years, no history of intake of vitamin C or other antioxidant vitamins at least three months prior to start of study and absence of diabetic complications, were included in the study. Patients with other types of diabetes and systemic diseases, pregnancy, lactating mothers, smokers, altered LFTs and RFTs were excluded. All patients were thoroughly examined by the consultant diabetologist to rule out the presence of complication(s) clinically before subjecting them to laboratory investigations at baseline and at the end of three months that is evaluation of fasting blood sugar, random blood sugar and glycosylated hemoglobin from Pathology laboratory of NMC, on Roche Cobas 6000 series (c 501) chemistry analyzer. Vitamin C analysis was performed at the Multidisciplinary Research laboratory (MDRL) of BUMDC by Human Vitamin C ELISA kit number DRE67468, Glory science, China. The calculated sample size was 140 by using the formula for prevalence. After obtaining written informed consent a total of n=160 were enrolled and divided into control group and treatment group with 80 participants each using sealed envelope technique. The patients in treatment group were prescribed vitamin C 500 mg twice daily per orally for three months along with their oral antidiabetic drugs. The patients in control group were prescribed the same except vitamin C. All patients were advised for life style changes with standard dietary charts for type 2 diabetes mellitus and 30-40 minutes brisk walking daily. The oral antidiabetic drugs included combination therapy which dipeptidyl peptidase 4 (DPP4) inhibitors and metformin in 50/500 or 50/850 mg twice daily depending upon there glycemic index. The data was entered on SPSS version 23 for data analysis. The results were expressed as mean ± standard deviation (SD). After checking the normality of data the comparison between treatment group and control group was performed by independent sample t test. Paired analysis in between the treatment group was done by paired sample t test. The Pearson's correlation was applied to determine the relationship between vitamin C and HbA1c, FBS and RBS variables. After checking Pearson's correlation linear regression was analyzed. Significant differences were considered at p value<0.05.

RESULTS:

Total n=140 subjects completed the study and their data was analyzed for present study. Chi square homogeneity test revealed no significant difference in duration of diabetes mellitus between control and treatment group. The age of treatment group and control group ranged from 40 to 65 years with a mean of 50.65±7.96 and 50.58±9.10 respectively. From 140 subjects 82 (59%) subjects were females and 58 (41%) were males. Anthropometric measurements (pulse, BMI, blood pressure, weight and height) showed no significant difference between control and treatment groups.

The Paired sample t test was applied for the analysis of paired observations of fasting blood sugar, random blood sugar, HbA1c and vitamin C between day 0 and day 90. Table 1 shows the comparison of glycemic parameters between day 0 and day 90 of treatment group. The vitamin C level at day 0 in treatment group was 0.25 mg/dl and at day 90 was 1.4 mg/dl. There was significant difference ($p<0.001$) in levels of FBS, RBS and HbA1c at day 90 in treatment group after administration of vitamin C 500 mg twice daily for three months.

The comparison of glycemic parameters between control and treatment group was performed by Independent sample t test. Table 2 shows the results of glycemic parameters and vitamin C comparison between control and treatment group.

AST level showed significant difference but there was no significant difference in ALT and bilirubin in treatment group at three months after administration of vitamin C however ALT, AST and bilirubin showed insignificant difference between control and treatment group. RFTS (urea and creatinine) showed non- significant difference between control and treatment group and in between treatment group.

The Pearson's correlation coefficient was used to determine the association between independent variable vitamin C and dependent variables FBS, RBS and HbA1c. Table 3 shows the results of Pearson's correlation between vitamin C and FBS, RBS and HbA1c. There was a statistical significant moderate negative correlation between vitamin C concentration and HbA1c levels r_s= -0.465, p< 0.001; statistical significant weak negative correlation between vitamin C concentration and RBS levels r_s = -0.364, p = 0.002; statistical significant moderate negative correlation between vitamin C concentration and FBS levels r_s = -0.435, p< 0.001.

Linear regression was performed to check the degree of association of independent variable vitamin C and dependent variables FBS, RBS and HbA1c. Table 4 shows the results

of linear regression. A linear regression was established that vitamin C given for three months in divided doses of 500 mg twice daily accounted for 27.4% of variation in fasting blood sugar with adjusted R^2=26.3%; 23.6 % variation in random blood sugar with adjusted R^2= 22.5% and 37 % variation in HbA1c with adjusted R^2 = 36.1%. Vitamin C given for three months in divided doses significantly reduced FBS levels, F (1,70) = 26.4, p<0.001; RBS levels, F (1,70) = 21.6, p<0.001 and HbA1c levels, F (1,70) = 41.1, p< 0.001.

Table 1: Treatment group comparison between day 0 and day 90 of laboratory parameters (N=70)

Parameter	Day 0 (Mean ± SD)	Day 90 (Mean ± SD)	P-value
FBS (mg/dl)	139±29	125±25	P<0.001
RBS (mg/dl)	208±45	187±34	P<0.001
HbA1c (%)	7.9±0.5	7.5±0.7	P<0.001
ALT (IU/L)	31.8±7.1	31.6±6.1	0.84
AST (IU/L)	24.6±6.5	23.0±5.8	P<0.05
Bilirubin (mg/dl)	0.6±0.1	0.6±0.1	0.55
Urea (mg/dl)	31.5±7.8	30.4±7.1	0.09
Creatinine (mg/dl)	0.8±0.1	0.7±0.1	0.64
Vitamin C (mg/dl)	0.25±0.29	1.42±0.91	P < 0.001

Key: FBS: Fasting blood sugar, RBS: Random blood sugar, HbA1c: Glycosylated hemoglobin, ALT: alanine aminotransferase, AST: aspartate aminotransferase *N= Number of subjects, Test applied: Paired sample t test

DISCUSSION:

About 25 % of the newly diagnosed patients already have developed one or more complications of diabetes mellitus.[12] Hyperglycemia in long standing diabetes mellitus is a continuous source of oxidative stress which plays an important role in development of complications. Oxidative damage leads to production of glycosylated products and other advanced glycation end products (AGEs). Lipid peroxidation also occurs as a result of long standing hyperglycemia.[13] Other pathways implicated in increased oxidative damage in type 2 DM include glucose auto-oxidation, polyol pathway and protein kinase isoforms activation.[14] These all processes are continuous source of oxidative damage leading to endothelial damage and micro vascular complications.[15] Along with increased oxidative stress in type 2 DM the antioxidant system is also not functioning as the levels of antioxidants is less. Vitamin C is an important antioxidant that helps to diminish the oxidative damage and plays an important role in various reactions.[16] It is hydrophilic and soluble in water. Humans are unable to synthesize vitamin C endogenously as they lack L-gluconolactone oxidase.

Vitamin C is a six carbon lactone ring with 2,3- enediol moiety which provides antioxidant properties. It has structural similarity to glucose and replaces many reactions in the body.[17] This vitamin, also called as ascorbic acid, was discovered by Hungarian biochemist Albert Szent Gyorgyi and is involved in many important functions in the human

Table 2: Comparison of laboratory parameters between control and treatment group at day 0 and 90 (N= 140)

Parameters	Control group		Treatment group		P value
	Day 0 (Mean±SD)	Day 90 (Mean±SD)	Day 0 (Mean±SD)	Day 90 (Mean±SD)	
FBS (mg/dl)	142±25	141±20	139±29	125±25	<0.001
RBS (mg/dl)	202±41	195±34	208±45	187±34	>0.05
HbA1c (%)	7.7±0.6	8.4±0.8	7.9±0.5	7.5±0.7	<0.001
ALT (IU/L)	30.5±10.4	29.25±7.1	31.8±7.1	31.6±6.1	0.60
AST (IU/L)	24.5±8.7	23.1±5.6	24.6±6.5	23.0±5.8	0.93
Bilirubin (mg/dl)	0.5±0.2	0.5±0.1	0.6±0.1	0.6±0.1	0.08
Urea (mg/dl)	30.9±8.0	31.0±8.1	31.5±7.8	30.4±7.1	0.40
Creatinine (mg/dl)	0.8±0.1	0.7±0.1	0.8±0.1	0.7±0.1	0.69
Vit C (mg/dl)	0.26±0.45	0.25±0.36	0.25±0.29	1.4±0.9	<0.001

Key: FBS: fasting blood sugar, RBS: Blood sugar random, HbA1c: glycosylated hemoglobin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Test applied: Independent T test

Table 3: Pearson's correlation coefficient between independent variable vitamin C and dependent variables HbA1c, RBS and FBS in treatment Group

Independent variable	Dependent variable	Correlation coefficient (r_s)	P value
Vitamin C	HbA1c	-0.465	<0.001
Vitamin C	RBS	-0.364	0.002
Vitamin C	FBS	-0.435	<0.001

Figure1: Scatter plot with line of best fit showing R^2 linear = 0.370 between vitamin C (mg/dl) and HbA1c (%)

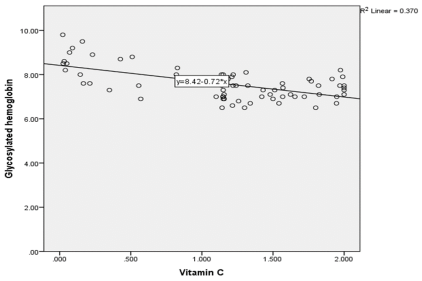


Figure 2: Scatter plot with line of best fit showing R^2 linear = 0.236 between vitamin C (mg/dl) and random blood sugar (mg/dl)

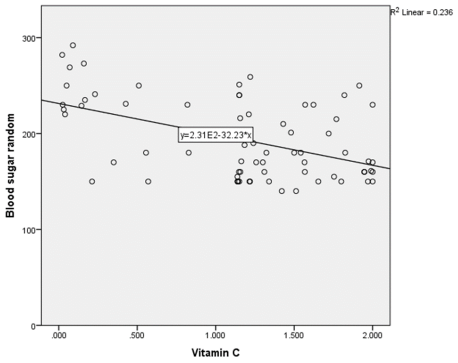
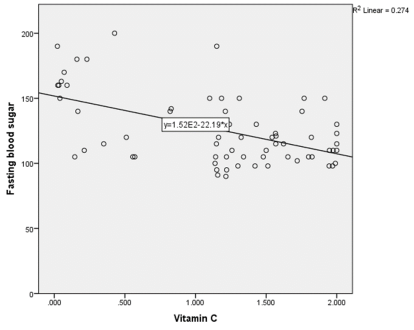


Figure 3: Scatter plot with line of best fit showing R^2 linear = 0.274 between vitamin C (mg/dl) and fasting blood



body. Antioxidant activity plays an important part in scavenging free radicals.[18] It is also needed in tissue repair processes. Dietary sources are the natural means of ascorbic acid of which the citrus fruits and green leafy vegetables are richest source. Other sources include animal food of which the liver is important source. Animals usually synthesize this vitamin which then concentrates in the liver. The estimated average requirement (EAR) of vitamin C for adult men and women age = 19 years is 30 mg/day while recommended dietary allowance (RDA) for adult men and women aged = 19 years is 45 mg/day. The upper intake level which has no adverse effects for adult men and women aged = 19 years is 2000 mg/day.[19]

Hence this study was conducted to evaluate the effects of vitamin C therapy along with oral hypoglycemic drugs on the glycemic indices in type 2 diabetic patients and to find out the correlation of vitamin C with the glycemic indices.

The present work showed that vitamin C administration in a dosage of 500 mg along with antidiabetic drugs decreased the fasting blood sugar, random blood sugar and HbA1c after three months. This work is supported by the study of Ali et al., in which significant difference ($p<0.05$) was seen in the FBS and HbA1c both between treatment and control groups and within the treatment group.[20] Mason et al. found non-significant difference in FBS and HbA1c after 4 months of administration of vitamin C 500 mg twice daily contradictory to our study but found significant difference in random blood sugar supporting our study.[21] Gillani et al., also found significant difference in FBS and HbA1c after administration of 500 mg once daily vitamin C for 12 months.[22] Okafor et al. found significant differences in random blood sugar after administration of vitamin C 600 mg thrice daily in a treatment group.[23] Our study showed similar and non- significant difference in AST results in both groups. Urea and creatinine in present study showed no significant difference in between the treatment group and control group indicating that co-administration of Vitamin C with oral hypoglycemic drugs is safe for use and does not produce any untoward effects in the diabetic patients upon administration. Ali et al., also found similar results for ALT, AST, urea and creatinine in their study.[20] Mason et al., found supporting results with our study in which there was no significant difference compared to control group.[21] This study found moderate negative correlation between vitamin C and FBS. Mahmouabadi and Rahbar also found significant negative correlation between vitamin C and FBS. They also found significant reduction in HbA1c by 9%.[24] In our study HbA1c was reduced by 0.4% in the treatment group. Another study by Kotb also showed significant negative correlation between vitamin C and FBS in which FBS was reduced by 25mg/dl after three months of administration of vitamin C, whereas we have found a reduction of 14mg/dl. They also found significant reduction in random blood sugar by 20mg/dl, whereas we have observed a decline of 21mg/dl and in HbA1c there is a reduction of 1.59%.[25] However in our study, HbA1c was reduced by 0.4% as mentioned above. This could be because of more strict diet control and pattern of exercise followed by the patients of Kotb in comparison to our study. This study was done at a single center and was an open label clinical trial with small sample size.

CONCLUSION:

Co-administration of vitamin C with oral antidiabetic therapy has produced beneficial effects on the glycemic indices by reducing them from baseline. Negative correlation has been found between vitamin C and glycemic indices. Future studies with large sample size and at multiple centers may be conducted to authenticate the results of present study.

Authors Contribution:
Erum Behroz Khan: Concept, Study Design and Critical Revision
Samar Fatima: Drafting, concept, study design, data analysis and interpretation
Mairah Shah: Data Analysis
Zuhair Ahmed: Data interpretation
Sohail Khan: Data Analysis
Sunia: Data interpretation

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Orginal Article

Open Access

Impact of COVID-19 Lockdowns on Patients Undergoing Orthodontic Treatment

Erum Behroz Khan, Samar Fatima, Mairah Shah, Zuhair Ahmed, Sohail Khan, Sunia

ABSTRACT:

Objective: To determine the awareness of regular orthodontic follow-up visits among the patients. The secondary objective was to assess patients' perception towards orthodontic treatment needs and their psychological status during lockdown.

Study Design and Setting: This cross-sectional study was conducted at Sindh Institute of Oral Health Sciences, (JSMU) from August, 2020 to January, 2021.

Methodology: The questionnaire contained 15 questions divided into 3 categories. First category was about the awareness of routine checkup among patients Q1-Q5, second was to assess the impact of lockdown on patients' visit to orthodontist Q6-Q12 and third was to assess the psycho-social effect of lockdown Q13-Q15. Three point likert scale was applied on each question with cut off value set as 70% for the 3 categories to get positive/negative response. SPSS version 22 was used for data entry and analyzing. Percentages and frequencies were calculated for qualitative variables like age, gender and educational level. Chi-square test was applied on all the three categories keeping the p-value <0.05 as significant.

Results: The study included 115 subjects comprising of 21(18.3%) males and 94(81.7%) females, aged 12-30 years with mean age 19.15±3.96. Out of 115 patients 47(40.9%) patients met the 70 % cut off criteria for category 1.Similarly, for category 2, 73(63.5%) patients met the 70% cut off value. For category 3, 7(6.1%) patients met the 70% cut off value. Statistically significant difference was found for category 1 with age, gender and educational level at p-value<0.05. Similarly, in category 3, only educational level showed statistically significant association.

Conclusion: The patients were quite aware of the need to visit orthodontists for regular follow ups during their treatment. The psychological status of the patients was the prime concern of the orthodontists as they had not sought orthodontic help during this time.

Keywords: COVID-19, Lockdown, Patients' Psychology, Treatment needs.

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INTRODUCTION:

The epidemics of Corona virus disease (COVID-19) was originated from Wuhan (China) in December 2019.The Chinese Center for Disease Control and Prevention considered novel Corona virus as the official causative pathogen for this disease on 8, January 2020.This virus was named initially as 2019-NCoV-2 [1, 2] and officially as severe acute respiratory syndrome Corona virus 2 (SARS CoV-2).The World Health Organization (WHO) on January 30, 2020 declared this virus outbreak as medical emergency internationally as it was a challenging public health problem prevalent throughout the world.[3] On March 27, 2020 WHO reported an update on COVID-19 i.e more than 500,000 cases and 23000 deaths. The COVID-19 outbreak originating from China spread exponentially throughout the world as major public health crisis.[4,5,6]

On 26,February 2020 Pakistan confirmed the COVID-19 two cases i.e a student in Karachi who had just returned from Iran and another case in Islamabad. The province of has recorded the most cases at about 134,000, and has also recorded the most deaths due to COVID-19, about 2,500

till April-2021. The country was put under a nation-wide lockdown from March 24th7.[8,9] Upon its end officially on 1st-May, the lockdown was eased in phases.[8,9]

In the dental OPD, the dentists, dental assistant and patients are at increased risk of getting infected with the virus due to the aerosols produced from using high speed hand-piece or doing ultrasonic procedures.[10] There is close contact with patients during performing orthodontic procedures. The main transmission routes for the spread of COVID-19 disease were found as close contact and through droplets. According to the study it has been reported previously that in the School and Hospital of Stomatology, Wuhan University corona virus infected 9 dental practitioners. Therefore, to reduce the spread of this disease the dental hospitals and clinics attended only dental emergencies, with shut down of all other routine dental procedures including regular orthodontic procedures especially in the Hubei Province, since January 23, 2020. Thus, this pandemic interrupted the routine follow-up visits of orthodontic treatment. Furthermore, orthodontic emergencies, such extended wires and loose brackets affected some of the patients, but they could not get effective and timely help from the specialists.[11] With the increasing outbreak of the disease and rapid rise in cases due to COVID-19 pandemic several government throughout the world imposed complete lockdown. Public gatherings, travelling etc were banned. Schools, colleges, universities, private/government offices, several OPDs including dental clinics were closed. As a result only emergency treatment was given to the patients. Hence, without any prior notice orthodontic appointments were also ceased till further notice. In orthodontics, there are usually less encounter with emergencies than regular follow up appointments. However, the importance of monthly check-ups and routine orthodontic appointments has not been understood, as well as the impact of confinement and lack of orthodontic assistance during lockdown on patients in times of need should be determined.[12] The negative effects are produced on individuals and in the society due to the outbreak of any major epidemic.[13]

The rationale of this study was to determine whether or not the patients consider the regular orthodontic appointments as important as they were. These are the areas that need to be addressed. Therefore, the study was conducted, and a survey was done to assess the COVID-19 lockdowns' impact on patients who are undergoing orthodontic treatment.

This study was aimed to assess the COVID-19 lockdown's impact on patient's visit for orthodontic treatment needs and the psycho-social impact on them during lockdown.

METHODOLOGY:

This observational cross-sectional study was conducted at Sindh Institute of Oral Health Sciences, (JSMU) from August, 2020 to January, 2021. Non-probability consecutive sampling technique was used to enroll study participants. By using WHO calculator sample size was calculated by taking the response percentage as 17.6% from previous study[12], confidence level 95%, margin of error 7%, the calculated sample size was 115. Impact of COVID-19 lockdown on patients was assessed through a questionnaire used in a study [10] with slight self -modification. It was distributed to orthodontic patients visiting dental OPDs as per appointment. Online questionnaire was also used for those who have access to internet and computer. The questionnaire contained 15 questions divided into 3 categories i.e first category would assess the awareness of routine checkup among patients Q1-Q5, second would assess the impact of lockdown on patients' visit to orthodontist for treatment needs Q6-Q12 and third would assess the psycho-social effect of lockdown on their treatment Q13-Q15. Three point likert scale was applied on each question with cut off value set as 70% for the 3 categories to get positive/negative response. Inclusion criteria were, both genders with age range of 13-30 years, patient presenting with complain of mal-aligned teeth and undergoing orthodontic treatment. Exclusion criteria was previously treated orthodontically patients were not enrolled for the study. Institutional Review Board of Jinnah Sindh Medical University provided the ethical approval for this study. Proper written informed consent was taken from all the adult patients and for children it was taken from their guardians. SPSS version 22 was used for data entry and analyzing. Percentages and frequencies were calculated for qualitative variables like age, gender and educational level. Chi-square test was applied on all the three categories keeping the p-value <0.05 as significant.

RESULTS:

The study included 115 subjects comprising of 21(18.3%) males and 94(81.7%) females, aged 12-30 years with mean age 19.15±3.96. Among all the subjects 7(6.1%) had primary level of education, 27(23.5%) had secondary level of education and 81(70.4%) had higher secondary educational level. Out of 115 patients 47(40.9%) patients met the 70 % cut off criteria for category 1 that shows that the patients had awareness regarding regular follow up visits during lockdown. Similarly, for category 2, 73(63.5%) patients met the 70% cut off value showing the impact of lockdown on patients' visit to orthodontist for treatment needs. For category 3, 7(6.1%) patients met the 70% cut off value showing that the lockdown had psycho social impact on them. No statistically significant difference was found for category 1 with age, gender and educational level. Category 2 showed statistically significant association with age (p-value=0.002), educational level (p-value=0.001) and highly significant association with gender (p-value=0.000).Similarly, category 3 showed statistically significant association only with educational level (p-value=0.003).

DISCUSSION:

This lockdown has caused many difficulties for the patients undergoing orthodontic treatment. This study aimed to assess

Table 1: Responses to the Questionnaire in Frequency and Percentage

QUESTION	AGREE	NEUTRAL	DIS AGREE
1. Has it been more than 2 months since you visited your orthodontist?	113(98.3)	0(0)	2(1.7)
2. Are you worried that you are not getting to go for regular follow ups for your treatment?	103(89.6)	5(4.3)	7(6.1)
3. Are you following all the instructions given by your orthodontist, such as wearing of elastics and other oral hygiene instructions?	106(92.2)	9(7.8)	0(0)
4. Have you been in touch with your orthodontist?	46(40)	8(7)	61(53)
5. Does your orthodontist check on you regularly?	18(15.7)	9(7.8)	88(76.5)
6. Are you worried regarding your treatment that it will take more time now?	107(93)	2(1.7)	6(5.2)
7. Since the lockdown started, have you had any problems with anything fixed in your mouth (eg, brackets, elastics, appliances and plates)?	74(64.3)	4(3.5)	37(32.2)
8. Are poking wires, broken brackets and elastics coming out of mouth the most common problems you have faced?	79(68.7)	2(1.7)	34(29.6)
9. Have you suffered from any emergency such as pain, swelling, lacerations/ cuts, etc., due to treatment since the lockdown?	56(48.7)	7(6.1)	52(45.2)
10. Do you think that orthodontic treatment should be considered an emergency?	57(49.6)	14(12.2)	44(38.3)
11. Do you think this lockdown is affecting you more than your orthodontist?	64(55.7)	41(35.7)	10(8.7)
12. This lock down has made you to realize the importance of being regular with your appointments?	112(97.4)	0(0)	3(2.6)
13. Do you think about your treatment cost will increase following the lockdown?	26(22.6)	20(17.4)	69(60)
14. Following this lockdown, do you plan to visit your orthodontist as soon as possible?	113(98.3)	1(0.9)	1(0.9)
15. Are you scared to visit your orthodontist after the lockdown ends?	23(20)	5(4.3)	87(75.7)

the treatment progress expectations, regular follow up awareness, emergency considerations and the psycho-social impact of lockdown on patients. The study results revealed that most of the patients faced difficulties due to lack of access to orthodontic care.

Total 98.3% patients revealed that it had been more than 2 months since they last visited their orthodontists. The biggest challenge faced by orthodontic patients is to maintain their oral hygiene. The accumulating plaque around the fixed orthodontic appliance results in demineralization i.e white spot lesions around brackets and bands leading to carious lesions.[14] If patients do not strictly follow the oral hygiene instructions due to prolonged treatment duration, then the plaque accumulation is inevitable. Therefore it is necessary to for orthodontic patient to visit dental OPD on regular basis so that the orthodontist can have check on their current plaque accumulation and oral hygiene status. Subsequently, planning for the management.[15-17]

The regular follow up visits are also important for the treatment progress for most of the mechanics applied in orthodontics. For example, the elastics used for retraction or for closing the extraction spaces can become loose or tear. Even plaque accumulation can take place around these elastics leading to caries and ultimately effecting the treatment. But, these problems are mostly ignored by the patients. Poking wires, loose bands/brackets and lacerations/cuts are usually noticed by patients as inconvenient which can have negative effect on orthodontic treatment.

Orthodontic emergencies or appointments were most commonly due to the loosening of bondable buccal tubes or brackets, followed by the loose bands as stated by Rajesh Gyawali et al.[18] The other possible reasons were, detachment of buccal tubes from the band, tearing of bands, trauma caused by the overextended distal wire to the mucosa, loose ligature ties, dislodgement of elastomeric chains and breakage of acrylic plates.[18] Total 68.7% of the patients reported in our study that they had commonly faced problems regarding poking wires, broken brackets and loose elastics as compare the study that stated that most of the patients did not face any problems. Approximately 48.7% patients had pain, swelling, lacerations and cuts due to orthodontic treatment. Relating this to the same study, most of the patients did not had any pain, swelling, lacerations and cuts.[12] In a study Caprioglio et al and Suri et al advised some methods to deal

orthodontic emergencies by the patient themselves i.e they can cut the over-extended poking wires through nail cutters, or can also apply disclosing wax that is available over the counter for relief, and through assistance virtually.[19, 20]

As stated by Rokyo et al that compliance and the length of the orthodontic treatment and the patient's compliance were inversely proportional to each other that is compliance is weak in case of longer treatment durations and vice versa. Therefore, there is a possible chance for the reduction in compliance of patients during the lockdown, though in the current study, 92.2% of patients reported that they were following all instructions previously given to them.[16] Total 89.6% patients were worried regarding their loss to follow up visits due to lockdown, which can be the most commonly due to anticipated increase in the treatment duration (93%). This shows the awareness regarding importance of the need for regular appointments i.e 97.4% of patients stated that the lockdown had made them realize the importance of regular follow-ups.

Total 5.2% of patients were not worried about their treatment, the probable reason can be that those had some external motivation and lack active interest in the treatment, or patients who did not encounter any problems during this pandemic lockdown (32.2%)..However, this does not represent the majority of patients affected. Total 40% patients were in contact with their orthodontists while 53% were not. The reason for these results could again be the lack of interest, fear of orthodontic treatment, or could be the problems faced by them during their treatment. Another possible reason could be the lack of access to the orthodontist i.e unavailability of transport or facility, instead of need. From orthodontists' perspective following-up on their patients as much as possible is also necessary, 76.5% of the patients stated that no calls were received from their orthodontists. This reflects that the orthodontists should be kept in touch with their patients as they are confined to their homes and are worried as they are not getting timely treatment. Small gestures like regular check-up calls can reduce the worry and boost confidence, and give patients reassurance that they are not helpless in this time. This gives the sense of care from orthodontist to the patient. Total 55.7% of the patients thought that they had been affected by the lockdown more while 35.7% of the patients thought that both the patient as well as orthodontist was equally affected. This reflects the patients' sympathetic behavior towards the orthodontist during lockdown. When the patients were asked about that orthodontic treatment should be considered as an emergency, results revealed that 49.6% of the patients considered the problems faced by them as emergency while 38.3% did not.

A small number of patients reported the fear of increased cost of treatment, i.e 22.6% shows that the orthodontist should re-ensure patients that, the treatment cost will remain the same if no additional treatment is required (with patients' consent) even post lockdown. And, if any additional cost is increased, it would be utilized for personal protection equipment to ensure safety for both the patient and health care professional.

Total 75.7% of patients replied that they had no fear at all to visit their orthodontist after the lockdown, the possible explanation for this can be the lack of awareness of the various transmission modes possible for spread of diseases in a dental office with aerosols, close contact of doctors with the patients, etc.[21] Finally, 20% of the patients showed that they were more concerned about the worldwide COVID-19 pandemic. This study thus highlights these patients as they are more concerned about their health, does not consider orthodontic treatment important during lockdown. So, to reassure these patients they should be taken in confident that proper protective measures will be taken to limit the transmission of disease.

CONCLUSION:

The patients were quite aware of the need to visit orthodontists for regular follow ups during their treatment. The psychological status of the patients was the prime concern of the orthodontists as they had not sought orthodontic help during this time.

Authors Contribution:
Erum Behroz Khan: Concept, Study Design and Critical Revision
Samar Fatima: Drafting, concept, study design, data analysis and interpretation
Mairah Shah: Data Analysis
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Original Article

Open Access

Refractive Error in Juvenile Patients Presenting with Nystagmus at Tertiary Care Hospital of Karachi

Kanwal Perveen, Nasir Ahmed, Khalida Perveen, Tauseef Mehmood

ABSTRACT

Objective: To evaluate the types of refractive errors in nystagmus patients among the age (5-15 years) patients.

Study Design and Setting: An observational cross-sectional study was conducted at Pediatric department of Al-Ibrahim Eye Hospital, Karachi from June 2018 to March 2019.

Methodology: A total of 55 patients (110 eyes) were selected from study setting. The protocol for examination for all patients were evaluated at the special clinic of Orthoptics includes the demographic data, educational status, history of onset, type of nystagmus. The anterior segment was examined with a slit-lamp to exclude any other ocular disease. Orthoptic assessment includes cover uncover test, Hirschberg, ocular motility, prism cover test and pupillary reflex test, to observe any associated deviation. All the patients were examined after obtaining a fully informed consent. After the proper diagnosis of nystagmus patient was recruited as per inclusion and exclusion criteria with no restrictions of gender. All the observations were noted on a Proforma, Data analysis was done by using SPSS version 20. P-value <0.05 was considered as statistically significant.

RESULTS: A total of 55 patients, 29 male (52.7%) and 26 female (47.3%) were selected. This study shows out of 55 patients (110 eyes), 46 (42%) eyes had myopic astigmatism, while 33 (30%) eyes were found hyperopic astigmatism, 20 (18%) eyes were observed hyperopic and 11 (10%) eyes were observed myopic.

CONCLUSION: Most common type of refractive error in nystagmus was myopic astigmatism. The refractive correction should be encouraged in children with nystagmus; improvement in visual function is likely to occur.

KEYWORDS: Oscillation, Pendular Nystagmus, Refractive error

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INTRODUCTION:

Nystagmus is a congenital or acquired uncontrolled eye movement results in vision loss. Also known as dancing eye". OR oscillating eye movement with rhythm is known as nystagmus.[1,2] Types of oscillations, pendular nystagmus may be due to sinusoidal oscillations in which equal amplitude and velocity of movement occurs, jerk nystagmus in which a sluggish starting phase and a fast corrective phase.[3] In physiologic nystagmus minimized retinal image slip, where the slow phases of nystagmus is present but the slow phases of pathologic nystagmus cause maximum retinal image slip. Greater than 5 degree Retinal image slip of per second produces a decline in visual acuity.[4,5] In study of United Kingdom shows developed rate of occurrence of nystagmus in white Europeans than Asians. The prevalence of nystagmus in the general population was estimated to be 24.0 per 10,000 populations.[6] The study based on mass screening in china shows prevalence of congenital nystagmus was1:1404.[7] Nystagmus was found to be a leading cause of low vision in study sample comprising of 504 individuals.[8] There are three main mechanism of eye movement control: fixation, the vestibulo-ocular reflex and gaze holding system. Any disorders which cause failure in any of these will results in nystagmus.[9] There are three forms of nystagmus Infantile: Most often develops by 2 to 3 months of age, Spasmus nutans: It usually occurs between 6 months and 3 years of age and improves on its own between 2 and 8 years of age. Acquired: Develops later in childhood or adulthood.[10] An error in the focusing of light by the eye is known as refractive error.[11] Uncorrected refractive error caused estimated a total of 153 million people visually impaired.[12] In a retrospective data of 47 medical records of children with infantile nystagmus syndrome spherical equivalent of Hypermetropic refractive error was mostly found.[13] A study in 2010 data

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shows with the rule astigmatism was predominant in children with infantile nystagmus syndrome.[14] This study will help us to identify the most frequent occurring refractive error in patients with nystagmus as related studies have not been conducted yet in the Sindh province. Therefore; the purpose of this study was to evaluate the types of refractive errors in nystagmus patients among the age (5-15 years).

METHODOLOGY:

This was a cross-sectional study carried out at Pediatric department of Al-Ibrahim Eye Hospital, Karachi from June 2018 to March 2019. Prior Ethical approval was taken from the Institute Research Ethical Committee. A non- probability convenience sampling method was used to collect data. Sample size was calculated from WHO calculator by taking statistical formulation of 95% confidence interval and 5% margin of error. The sample size was determined by formula was 110. A total of 55 patients (110 eyes) were selected from patient attending Paediatric Department of Al-Ibrahim Eye Hospital, Karachi. The protocol for examination for all patients were evaluated at the special clinic of Orthoptics includes the demographic data, educational status, history of onset, type of nystagmus. The anterior segment was examined with a slit-lamp to exclude any other ocular disease. Orthoptic assessment includes cover uncover test, Hirschberg, ocular motility, prism cover test and pupillary reflex test, to observe any associated deviation. All patients were examined and data was recorded after obtaining a fully informed consent from their guardian and data confidentiality was ensured. After the proper diagnosis of nystagmus patient was selected with inclusion and exclusion criteria with no restrictions of gender. Age group was 5-15 years was followed. Exclusion criteria were any ocular surgery that may cause nystagmus, pseadophakic, Aphakic and patients with other ocular pathologies and degenerations. All the observations were noted on a proforma, Cycloplegic refraction was done in both eyes of one participant and 3 drops of cyclopentolate eye drop were administrated and then later Retinoscopy was performed to assess the types of refractive error in nystagmus patients. In Proforma researcher recorded age of patient, gender of patient, onset of nystagmus, type of nystagmus and wave form of nystagmus. The collected data was analyzed from the software SPSS version 20.0 Frequencies and percentages were calculated for the categorical variables. Different statistical charts were presented for several categorical data. P-value <0.05 was considered as statistically significant.

RESULTS:

A total of 55 patients (110 eyes) were selected on the basis of the inclusion and exclusion criteria of the study, from which 58(eyes) were of male (52.7%) and 52 (eyes) were of female (47.3%), both genders, all having nystagmus. The age group was divided into two categories (5 to 10 years) and (>10 to 15 years), from age group (5 to 10 years)10 (91%) eyes were found as myopic, 13 (65%) eyes were hyperopic, 35 (76 %) eyes were myopic astigmatism and 24 (73%)eyes were hyperopic astigmatism, while in age group (>10 to 15 years), 1 (9%)eye were myopic, 7 (35%) eyes were hyperopic, 11(24%) eye were myopic astigmatism and 9 (27%) eyes were hyperopic astigmatism. In comparison of onset of nystagmus out of 55 patients only 3 patients 6 eyes(5%) had acquired whereas 52 (104 eyes, 95%)patients had congenital nystagmus. In patients with congenital nystagmus, 11 (100%) eyes were found as myopic, 20 (100%) eyes were hyperopic, 42 (91%) eyes were simple myopic astigmatism, and 31 (94%) eyes were hyperopic simple astigmatism. In manifest type of nystagmus less common refractive error was myopia. From which 11 (100%) eyes were myopic, 18 (90%) eyes were hyperopic, 42 (91%) eyes were compound myopic astigmatism and 29 (88%) eyes were simple hyperopic astigmatism.

While in latent type of nystagmus there were no Patient found with simple Myopic but 2 (10%) eyes were hyperopic, 4(9%) eyes were compound myopic astigmatism and 4 (12%) eyes were compound hyperopic astigmatism.

According to waveform of nystagmus in jerky 11 (100%) eyes were myopic, 20 (100%) eyes were hyperopic, 46 (100%) were myopic astigmatism and 33 (100%) eyes were hyperopic astigmatism while there were no eyes with pendular waveform nystagmus.

Table 1: Demographic Characteristics

Age (Years)	**Frequency**	**Percentage**
5 - 10	41	74.5%
11- 15	14	25.5%
Total	55	100.0%
Gender	**Frequency**	**Percentage**
Male	29	52.7%
Female	26	47.3%
Total	55	100.0%
Education	**Frequency**	**Percentage**
Un-Educated	38	69.1%
Primary	16	29.1%
Secondary	1	1.8%
Total	55	100.0%

Figure 1: Types of Nystagmus Onset (n=110 eyes)

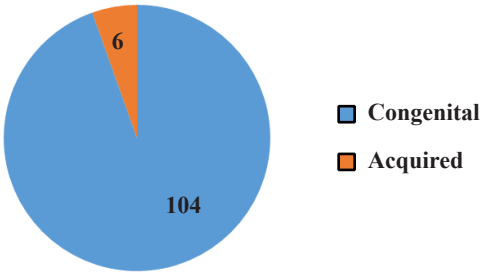

Figure 2: Type of Nystagmus (n=110 eyes)

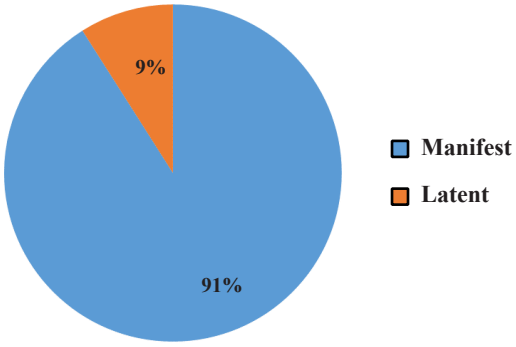

Figure 3: Type of Refractive Error (n=110 eyes)

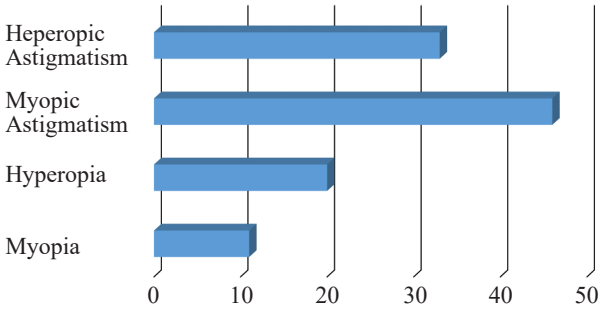

Table-2: Distribution of Type of Refractive Error and Age

Type Of Refractive Error	Age of patient (years)		Total	P-value
	5 to 10	11 to 15		
Myopia	10	1	11	0.479
	12.2%	3.6%	10.0%	
Hyperopia	13	7	20	
	15.9%	25.0%	18.2%	
Myopic Astigmatism	35	11	46	
	42.7%	39.3%	41.8%	
Heperopic Astigmatism	24	9	33	
	29.3%	32.1%	30.0%	
Total Eyes	82	28	110	
	100.0%	100.0%	100.0%	

DISCUSSION:

This study was to evaluate the types of refractive errors in nystagmus patients among the age (5-15 years). A study in 2011 data showed Out of total 170 Down Syndrome patients Nystagmus was observed in 18 patients.[15] Children with nystagmus had greater association of Myopia and astigmatism[16]. Some studies shows increment in Astigmatism with age[17] caused by constant oscillations of the eyeball.[14] It is suggested to give full correction which can help in better distinguish horizontal stimuli than vertical ones.[13_18_19]

This study shows out of n=55 patients 110 eyes (100%), n=46 (42%) eyes had myopic astigmatism, while n=33 (30%) eyes were found hyperopic astigmatism, n=20 (18%) eyes were observed hyperopic and n=11 (10%) eyes were observed myopic. Similar studies have been reported by researchers before but none in province Sindh. Study is done on patients having Down syndrome. Astigmatism was present in 72.4% of patients of Down syndrome.[11] Nystagmus was observed in 18 patients having Down Syndrome.[11] In another study showed slightly myopic in children adolescent and adults with idiopathic congenital nystagmus. There was more astigmatism in the albino (Albinism is inherited conditions in which there is a lack of pigmentation in the eyes and usually in the skin and hair as well) group (primarily with-the-rule; where the vertical meridian is steepest).[14] While In other study adolescent and adults myopic in albinos were less than idiopathic Congenital Nystagmus,[14-20] but in this recent study it no difference was found in type of refractive error result but study sample size was different. In our study only n=20 eyes were found hypermetric. While a Prospective study shows Hypermetropia is the most predominant error in the Infantile Nystagmus Syndrome.[9] In this study n=11 eyes had myopia which show low occurrence of myopia but as compare to European study the occurrence of myopia and astigmatism (especially with-the-rule astigmatism) was greater in children with nystagmus.[10,15]

CONCLUSION:

Most common type of refractive error in nystagmus was myopic astigmatism. The refractive correction should be encouraged in children with nystagmus; improvement in visual function is likely to occur.

Authors Contribution:
Kanwal Perveen: Conceived the study, Manuscript writing, Proforma development, correspondence in replying reviews of manuscript & Final review
Nasir Ahmed: Manuscript writing, Designing the study, Proforma development, Data collection & Final Review
Khalida Perveen: Help in Manuscript writing
Tauseef Mehmood: Designing the study, Statistical Analysis Help in Methodology, Proforma development, Data collection & Final review

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Orginal Article

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Frequency and Spectrum of Non-Malignant Lesions in Abdominal Hysterectomy Specimens

Talat Zehra, Syeda Atiya Batool Gardezi, Mahin Shams, Sumaira Zareen, Iram Kehkashan Khurshid, Zareen Irshad

ABSTRACT:

Objective: To determine the histological spectrum of non-malignant lesions in abdominal hysterectomy specimens from women of reproductive age group.

Study Design and Setting: This was a descriptive cross-sectional study carried out at a private hospital in Karachi from December 2018 to December 2019.

Methodology: The uterine specimens of patients (n=262) between the ages of 24 to 55 years were collected. Hysterectomies done due to any benign uterine disease were included in the study. Hysterectomies due to malignant causes were excluded. Pathological diagnosis was done on light microscopy using routine hematoxylin and eosin staining technique. Data collected during the study period included patient's age, clinical history/diagnosis and histological diagnosis. On receiving the hysterectomy specimens as per protocol, specimens were immediately put in 10% formalin, appropriately labeled for patient's name, gender, age and procedure. In histopathology lab, grossing of the specimens was done using standard protocols. Frequency and variables were analyzed by using descriptive statistics of SPSS-version 22.

Results: Total n=262 hysterectomies were received. Mean age of all the patients was 34.7 years ±7.8. Non-malignant uterine pathologies on histopathology included 124(47.7%) leiomyomas, 52(20%) adenomyosis, 32(12.3%) endometrial polyps, 16(6.2%) endometrial hyperplasia, 6(2.3%) endometritis, 3(1.2%) disordered proliferative endometrium and 1(0.4%) endometrial stromal nodule. Rest of the cases showed normal phases of endometrial cycle. Only two cases (0.76%) out of 262 received as clinically benign uterine disease, were diagnosed as malignant on histopathology.

Conclusion: Leiomyoma is the most common uterine pathology diagnosed in clinical setting as well as encountered at histopathological examination followed by Adenomyosis and endometrial polyps in women of reproductive age group in Pakistan.

Keywords: Adenomyosis, Benign pathology; Hysterectomy, Leiomyoma, Prevalence.

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INTRODUCTION:

Hysterectomy is the most commonly performed gynecological surgery secondary to menorrhagia which can lead to various long-term health risks. Abdominal hysterectomy is one of the most common surgical procedures performed in gynecological setup all over the world.[1] The incidence of hysterectomy in US is 5.38/1000 women. It may or may not involve adnexa along with and may be total, partial or subtotal type depending on indication. Certain non-malignant conditions such as fibroids, adenomyosis and endometriosis also leads to significant surgical, psychological and health related consequences in patients especially if done for non-neoplastic conditions. Some of the common indications are dysfunctional uterine removal of uterus which leads to symptomatic relief. Also, it's a definite treatment to bleeding, uterine fibroids, uterine prolapse, endometriosis and adenomyosis.[2,3,4] Post-surgical consequences in women include infection, abdominal hernia, wound dehiscence and infertility as well as in patients whose bilateral salpingo-oophorectomy is done in which lack of

ovarian hormones leads to severe lifelong health issues.

The spectrum of benign diseases in hysterectomy specimens include uterine leiomyomas, adenomyosis, endometrial polyps, endometrial hyperplasia, endometritis, disordered proliferative phase endometrium and endometrial stromal nodule.[4,5,6,7] Out of which most frequent pathology encountered is leiomyoma.[3,5,8,9,10]

Uterine leiomyoma is defined as benign tumor of smooth muscle origin. Incidence of leiomyoma is found to be different according to different studies and it ranges from 20.5-69%.[5,8,9,10,11] It is the commonest benign pathology which leads to menorrhagia, dysmenorrhea, infertility and recurrent abortions in women of reproductive age group. Pathogenesis is unclear but most common risk factors are obesity, insulin resistance, familial tendency, advancing age and hormone therapy.[2,3,4,7,11] Hysteroscopic or laparoscopic myomectomy are safe and effective treatment options, but in women who do not wish to retain fertility, hysterectomy is still the standard surgical option. However, hysterectomy has its short term and long term sequelae – 1 in 30 women have an adverse post-surgical effect and mortality may be between 0.4-1.1 per 1000 operations[3]. Non-surgical interventional treatments are uterine artery embolization, and high-frequency MR-guided focused ultrasound surgery.[12]

Adenomyosis is defined as presence of endometrial tissue within the myometrium. Incidence of adenomyosis is variable according to literature. Symptoms are pelvic pain (including dysmenorrhea, dyspareunia), menorrhagia and impaired fertility status.[2]

Endometrial polyps are abnormal growths from the uterine lining composed of glands, blood vessels and stroma. These are space occupying lesions, are variable in size and present with clinical complaints of dysfunctional uterine bleeding and infertility.[6]

Endometrial hyperplasia also presents with menorrhagia and intermenstrual bleeding and there's a significant risk of developing malignancy in this entity depending upon the histopathological criteria of complexity and atypia.[3,6,7] Chronic endometritis is a leading cause of infertility in young females. Prevalence rate is approximately 10-11% in patients who underwent hysterectomies due to benign conditions. Presentation of it is however mild clinical symptoms like vaginal discharge and mild pelvic pain.

This study was done to update data and to document the spectrum of non-malignant uterine pathologies diagnosed on histopathology examination as abdominal hysterectomy in women of child bearing age group leads to infertility, unnecessary financial burden and exposes the patient to postsurgical morbidities and detrimental psychosocial effects. Alternative treatment modalities should be considered, encouraged and practiced to avoid unnecessary surgical exposure followed by consequences. Hence; this study was aimed to determine the histological spectrum of non-malignant lesions in abdominal hysterectomy specimens from women of reproductive age group.

METHODOLOGY:

Cross-sectional study carried out at Yasmeen Syed Lab (Atia Zafar Hospital) in Karachi from December 2018 to December 2019 after getting approval by institutional ethical review committee with reference to ERC number 1/2020.The duration of study was one year. A total of 262 cases were included in study. All the uterine specimens of patients between the ages of 24- 55 years, received at the hospital during sample collection period and fulfilled our inclusion criteria were collected. The inclusion criterion was to include abdominal hysterectomies of reproductive age group women in which the clinical and histological diagnosis was found to be non-malignant. All vaginal hysterectomies, abdominal hysterectomies due to known malignant cause either uterine or non uterine and autolyzed or poorly fixed samples were excluded. Data collected during the study period included patient's age, clinical history/diagnosis and histological diagnosis. On receiving the hysterectomy specimens as per protocol,specimens were immediately put in 10% formalin, appropriately labeled for patient's name, gender, age and procedure. In histopathology lab, grossing of the specimens was done using standard protocols. The tissue sections cut from the paraffin blocks were 3-4µm in thickness. Tissue processing was performed. Pathological diagnosis was done on light microscopy using routine hematoxylin and eosin staining technique. The histological slides were examined by two consultant histopathologists independently. Frequencies and variables were analyzed by using SPSS-version 22. Categorical variables clinical diagnosis and histological diagnosis were summarized into percentages, and mean (standard deviation) was calculated for numerical variable like age distribution. Stratification was done with regards to age to control the effect modifiers.

RESULTS:

A total of 262 hysterectomy specimens were received during the study period. The age group of these patients was 24-55 years. Minimum age was 24 years while maximum age was 55 years. Mean age of all the patients was 34.7 years ±7.8. The patients were distributed into 3 age groups as seen in table 2. Group 1 included patients of 24-34 years of age, which comprised of n=152 out of 262 patients (58%). Group 2 included patients of 35-44 years which comprised n=83(31.6%) of sample size. Group 3 included patients of 45-55 years which comprised of n=27(10.3%) of sample size. Non-malignant uterine pathologies on histopathological examination revealed n=124(47.3%) leiomyomas, n=52(19.8%) adenomyosis, n=32(12.2%) endometrial polyps, n=16(6.1%) endometrial hyperplasia, n=6(2.3%) endometritis, n=3(1.1%) disordered proliferative endometrium and n=1(0.4%) endometrial stromal nodule. Rest of the cases showed normal phases of endometrial

cycle as per table 3 & Figure 1.Only n=2 (0.76%) cases received with benign clinical diagnosis were diagnosed as malignant on histopathology.

DISCUSSION:

In our study, the most common finding is leiomyoma. The leiomyoma incidence varies from 20.5% to 69% and the adenomyosis incidence varies from 7.5% to 47% in the literature [5,9,13,14,15] In a study done by Imam et al, incidence of leiomyoma was 29.04% while incidence of adenomyosis was 11.69%.[14] Study done by Baral R et al, revealed leiomyoma incidence as 48.6% and 10.3% incidence of adenomyosis.[16] Study done by Pradhan SB et al, reported; 60% incidence of leiomyoma and 14% incidence of adenomyosis.[15]Study by VV Sreedhar et al observed 20.5%

Table 1: Age Statistics

N	262
Minimum	24Years
Maximum	55Years
Mean	34.7
Standard deviation	6.56

Table 2: Age group distribution

Age groups	Frequency	Percentage (%)
24-34	152	58%
35-44	83	31.6%
45-55	27	10.3%
Total	262	100%

Table 3: Frequency of histopathological diagnosis

Histopathological diagnosis	**Frequency**	**Percentage**
Leiomyoma	124	47.3
Adenomyosis	52	19.8
Endometrial polyp	32	12.2
Proliferative phase endometrium	17	6.5
Endometrial hyperplasia	16	6.1
Secretory phase endometrium	9	3.4
Endometritis	6	2.3
Disordered proliferative endometrium	3	1.1
Endometrial stromal nodule	1	0.4
Endometrioid Carcinoma	2	0.76

Table 4: Comparative frequency of histopathological diagnosis with age

Histological diagnosis (%)	Age groups in years			Total
	23-34	35-44	45-55	
Leiomyoma	68	45	11	124
Endometrioid carcinoma	0	0	2	2
Adenomyosis	19	20	13	52
Endometritis	6	0	0	6
Secretary endometrium	4	5	0	9
Disordered proliferative endometrium	2	1	0	3
Endometrial hyperplasia	10	6	0	16
Endometrial polyp	29	3	0	32
Proliferative phase endometrium	13	3	1	17
Endometrial stromal nodule	1	0	0	1
Total	152	83	27	262

Figure 1, 2: Leiomyoma showing fascicles of smooth muscle cells (1). Adenomyosis showing endometrial glands and stroma within the myometrium (2)

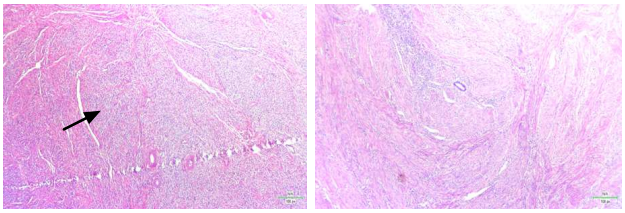


Figure 3: Endometrial polyp showing variably dilated endometrial glands surrounded by endometrial stroma and thick walled blood vessels

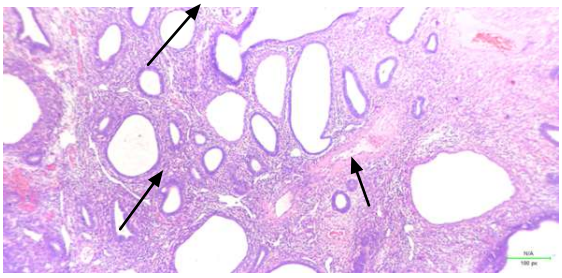


Figure 4,5: Proliferative endometrium(1) and Secretory endometrium(2)

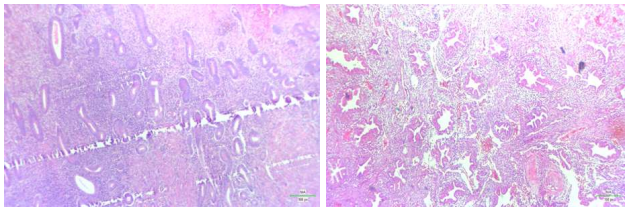
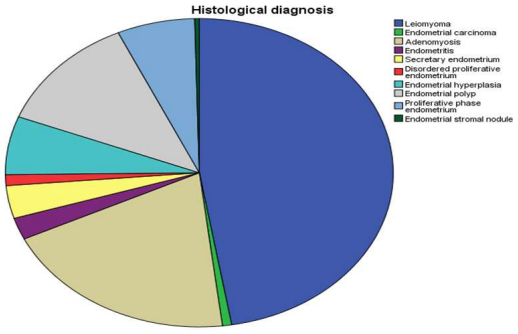


Figure 6: Histological Diagnosis



incidence of leiomyoma and 7.5% incidence of adenomyosis.[17] Incidence of leiomyoma was 69% while incidence of adenomyosis was 47% determined by study done by Sarfraz et al.[9] Incidence of leiomyoma was 44.7% while incidence of adenomyosis was 29.3% determined by Rauf et al.[18] According to all the above studies, leiomyoma ranks as most frequent among all the benign entities while adenomyosis the second frequent entity. Our study showed similar results in terms of most common histological diagnosis being leiomyoma (figure 1) and adenomyosis (figure 2). In our study, however the incidence of leiomyoma was 47.3% while the incidence of adenomyosis was 19.8%.

Our study was conducted with the aim of reporting morphological spectrum as well as frequency of benign lesions in abdominal hysterectomy specimens in women of child bearing age and to emphasize the importance of alternate treatment modalities to minimize the post-surgical consequences in these patients. The age range included in study was 24-55 years; maximum number of patients was seen in 24-34 years age group which is different from the literature review which shows commonest age group for hysterectomy is 40-50 years.[2,15,16] The studies done by Shams et al and Rauf et al shows maximum number of patients in 35-50 years and 41-50 years age group consecutively.[7,18]

Uterine leiomyoma is a benign tumor of smooth muscle origin and is by far the most common benign tumor of the uterus and constitutes the most frequently encountered entity in female genital tract. In postmortem examinations, it was detected in 50% of women. It leads to a spectrum of clinical presentations ranging from no symptoms at all to having severe menorrhagia, metrorrhagia and infertility. It is the most common benign pathology detected in hysterectomy specimens in many studies.[18,19,20,21]

Adenomyosis is characterized by the presence of endometrial glands and stroma within the myometrium. Patients are typically pre-or peri-menopausal women who present with abnormal bleeding. In adenomyosis, uterus becomes bulky and diffusely enlarged. It may accompany uterine leiomyomas. Adenomyosis is the second most common lesion encountered in our study and is the second most common lesion, as per literature review.[18,19,21,22]

Endometrial polyps are characterized by abnormal growths from the uterine lining composed of glands, blood vessels and stroma. These are space occupying lesions, are variable in size and are one of the leading causes of dysfunctional uterine bleeding and infertility. According to a study by Sajjad et al, incidence of endometrial polyp was 9%.[3]Another study conducted by Perveen et al specified the incidence of endometrial polyps 6.1%.[8] According to our study, incidence of endometrial polyp in child bearing age group is found to be 12.2% (figure 3).

Endometrial hyperplasia is characterized by increased gland to stroma ratio in endometrium. It leads to menorrhagia, metrorrhagia and post-menopausal bleeding in females. Increased risk of malignancy is associated with architectural complexity and cellular atypia. Studies done by Sajjad et al, Perveen et al and Shams et al documented incidence of endometrial hyperplasia 6% ,7.4% and 1.91% respectively.[6,7] Incidence of endometrial hyperplasia as per our study was 6.1%[6].

Other histopathological entities like chronic endometritis, disordered proliferative endometrium and endometrial stromal nodule also represent their fair share in morphological diagnosis[5] (figure 6).

Hysterectomy is the most common surgical procedure performed by gynecologists all over the world and its indication is variable for different regions.[1] The decision for abdominal hysterectomy in reproductive age group is very challenging for both patient and gynecologist and should be justified. The mean age of the patients who underwent hysterectomy in our study was relatively lower than the literature while leiomyoma frequency is comparable with the available literature. Our study is different from other studies because we haven't included malignancies in it and have focused on diversity of benign entities in the uterus. Alternative modalities like myomectomy should preferably be considered in women of reproductive age group.

The limitations of our study is the shortage of radiological findings. At our center, immunohistochemistry (IHC) is not available so we couldn't confirm the diagnosis on IHC although it didn't majorly affect the histological diagnosis.

CONCLUSION:

Leiomyoma is the most common uterine pathology diagnosed in clinical setting as well as encountered at histopathological examination followed by Adenomyosis and endometrial polyps in women of reproductive age group in Pakistan.

Authors Contribution:
Talat Zehra: Conceived and designed the study, collection and interpretation of data.
Syeda Atiya Batool Gardezi: Lierature Review, Analysis and interpretation of data, statistical analysis and drafting of article.
Mahin Shams: Analysis and interpretation of data, critical review of article for intellectual content
Sumaira Zareen: Critical revision of article for some intellectual content, final drafting
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Orginal Article

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Outcome of Early Removal of Urinary Catheter after Transurethral Resection of Prostate (TUR-P)

H. Mazahir Zulfiqar, Sajjad Ahmed, Zein UL Amir, M. Afzal Farooqui

ABSTRACT:

Objective: To determine the outcome of early removal of urinary catheter, and predict the possibility of TUR-P as a day care surgery, in terms of reduced hospital stay.

Study Design & Setting: It was a cross sectional study design with non-probability sampling conducted at Department of Urology, Rawalpindi medical college from January to July 2017.

Methodology: Total 190 patients fulfilled inclusion and exclusion criteria were selected for the study. Patient underwent TUR-P followed by catheter irrigation. Time was noted as 'zero' hour. The color of the effluent was grossly monitored. When the effluent became clear the catheter was removed and time noted. After successful voiding, patient was discharged and time noted. Success is if the duration from time 'zero' hours to catheter removal is within 24 hours and duration of hospital stay is within 36 hours. A time line greater is considered to be failure. Data analysis was done using SPSS version 15.0. For quantitative variables like age, time of catherization and hospital stay, median and standard deviation was calculated. For qualitative variables like success, frequency and percentages were calculated. Groups and tables were made to present the data.

Results: Mean duration of catherization after TUR-P is 9.67 ± 2.36 (hrs. min). Hospital stay was 26.73 ± 6.24 hours. Frequency and percentage of successful outcome was 152 out of 190 patients and 82.6% respectively.

Conclusion: Our study favors that in selected patients TUR-P can be performed with shorter hospital stay with minimal postoperative complications. This will benefit the patient in terms of reducing comorbids and considerable departmental financial savings.

Key Words: Trans-urethral resection of Prostate, Benign Prostatic Hyperplasia

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INTRODUCTION:

The gold standard treatment for obstructing enlargement of the prostate is Transurethral Resection of Prostate (TUR-P).[1] It provides the long-term benefit of improved voiding scores and variables[2] with reduced morbidity.[3] Enlarged prostate is a disease of older men.[4] Variables such as various co-morbidities and co-morbids as a result of the disease itself, such as urinary tract infections, effect of prolonged catherization, prolonged hospital stay add to the morbidity of such patients.[5] Attempt in modifying variables associated with the disease process can reduce the morbidity of the patient.

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The management of patients with enlarged prostate is dependent on the severity of the symptoms translated by the IPSS.[6] A mild score warrants watchful waiting with lifestyle modifications.[7,8] Moderate symptoms warrant the use of medical therapy and / or a combination of medical therapy options.[9,10] Severe symptoms, failure of medical therapy or developing complications as a result of prolonged obstruction warrants surgical intervention. Despite the availability of many minimal invasive surgical modalities, TUR-P remains the gold standard.[11]

Study conducted by Cheuk Fan Shum et al and Prasopsuk S. et al, proves that removal of the catheter on the first post operative day had a success of 98% with significant reduction in complications.[12, 13] J. Chander et al went further to remove the catheter on the same operative day after TUR-P without significant complications. [3]

TUR-P is an endoscopic modality that resects the prostatic lobes using either mono-polar or bi-polar current across a

resecting loop, using suitable fluid as irrigation.[11, 14] Post operatively; the effects of TUR-P can be assessed by follow up IPSS and uroflowmetry. [2, 15]

In this study setting; the protocol is patient after TUR-P is observed for a minimum of 5 days in hospital. On the fifth post-operative day the patient's catheter is removed and he is discharged after a successful trial of voiding per urethra. Due to scarce resources and a high volume of waiting patients for TUR-P this study addressed the impact of same day catheter removal after TUR-P with quality care and SOPs and its effects on hospital stay. This in turn is an attempt to decreased morbidity due to prolonged catherization, reduced hospital stay, waiting time and have less financial burden on patients and indeed was the rationale of the study. Hence; this study was aimed to determine the outcome of same day removal of urinary catheter after TUR-P, and predict the possibility of TUR-P as a day care surgery, in terms of reduced hospital stay.

METHODOLOGY:

It was a cross sectional study, conducted in the department of Urology and transplantation, Rawalpindi university medical college, from January to July 2017. One hundred and ninety patients were selected for the study using the WHO calculator. The variables used in the calculator were: confidence level 95%, anticipated populated proportion 98% [3], absolute precision required 2%. Non-probability sampling technique was used for patient selection. The inclusion criteria is, age greater than 40 years but less than 75 years[16], indications to proceed towards TUR-P[17], and prostate volume less than 50 grams on trans-abdominal ultrasound. Factors such as carcinoma of the prostate, hypertension, diabetes, and significant intra-operative complications such as urethral injury, bladder perforation or uncontrolled hematuria were excluded from the study.

Approval of the ethical committee was taken. Patients fulfilling the inclusion criteria were counseled and informed consent was taken. All patients selected for the study under went comprehensive evaluation including a complete history with evaluation of the international prostatic symptoms score (IPSS), clinical examination and basic laboratory and radiological investigations.[18] Ensuring fitness for spinal anesthesia and a negative urine culture, the patient was dated for TUR-P. After overnight admission, patient underwent conventional TUR-P.[14] A 24 Fr. 30 degrees, mono-polar, continuous flow, resectoscope with non-revolving sheath was used in all cases. Total procedure time did not exceed 60 minutes. After satisfactory resection, meticulous hemostasis was done and finally a check cystoscopy performed to ensure no residual prostatic chip remained in the bladder. At the end of the procedure a 22 Fr. three way silicone coated irrigation urethral catheter was passed and the balloon inflated, irrigation with 0.9% saline was started. This was noted to time 'Zero' hours.

In the post operative period pulse, blood pressure, temperature and oxygen saturation of the patient were monitored. Urine output per catheter was measured hourly by the formula of deducting the volume of urine output per catheter from the total volume of saline delivered as bladder irrigation. The colour of the effluent was grossly monitored by the naked eye till it became clear and transparent. At that time the irrigation is withheld for 1 hour, after which if the effluent remained clear the irrigation was stopped and the urethral catheter is removed. If the effluent does not remain clear, irrigation is resumed again.

After removal of the catheter, the patent was allowed to void per urethra. Symptom score (IPSS), hematuria and patient comfort on voiding are addressed. If all is well, the patient is discharged to follow up. Success is define as the duration from time 'zero' hours to catheter removal is less than 24 hours and the duration of hospital stay is less than 36 hours. A time line greater than expressed is considered to be failure.

Data analysis was done using SPSS version 15.0. For quantitative variables like age, time of catherization and hospital stay, median and standard deviation was calculated. For qualitative variables like success, frequency and percentages were calculated. Groups and tables were made to present the data. P-value <0.05 was considered as statistically significant.

RESULTS:

A total of 190 patients were enrolled in this study. Descriptive statistics of age (years) of the patient was calculated in terms of mean and standard deviation, tabulated in table 1. The time (hours. minutes) from time 'zero' to catheter removal was calculated in terms of mean and standard deviation. Mean time is 9.67 ± 2.36 (hrs. min). The post catheter removal IPSS showed a mean score of 34.69 ± 1.34. Hospital stay was measured in terms of hours. The mean hospital stay was 26.73 ± 6.24 hours. Success is defined as the time in hours, passed for catheter removal after 'zero' hour to be within 24 hours and satisfactory discharge from hospital within 36 hours. In our study, frequency and percentage of successful outcome were 152 out of 190 patients and 82.6% respectively. This is shown in graph 1. Effect modifiers like age were controlled by stratification, which was compared with the successful outcome in the study. Chi – square test was used and showed P value of 0.57, which was statistically not significant. This is shown in table 2.

DISCUSSION:

The prostatic gland lies between the two urinary sphincters, the bladder neck superiorly and the voluntary striated sphincter inferiorly. The prostate surrounds the prostatic part of the urethra. The gland is composed of zones; peripheral, central, transitional and fibromuscular stroma[19] Cystoscopically, the prostate can be viewed to have 2 lateral lobes and a median lobe.[20] Hyperplasia of the lobes leads to obstruction in the urinary flow that can progress to acute

Table 1:

Variables	N	Minimum	Maximum	Mean	Standard Deviation
Age (yrs)	190	41	75	64.4	7.35
Time to removal of catheter (Hr. Min.)	190	6.20	23.0	10.7	2.36
IPSS score, post TUR-P, post catheter removal	190	27	35	34.69	1.342
Hospital stay, post TUR-P. (Hr. Min.)	190	23.30	47.0	26.7	6.24

Graph 1: Frequency and percentage of Success.

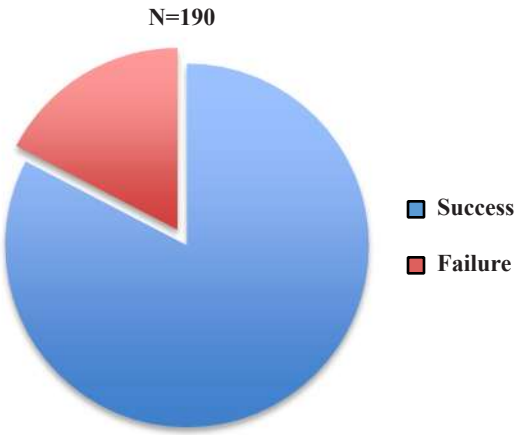

Table 2: Comparison of Age stratification with the success of TURP in the study

		Success		P-value
		Yes	No	
Age groups	< = 60 yrs.	43	12	0.576
		27.4%	36.4%	
	61 - 70 yrs.	79	15	
		50.3%	45.5%	
	above 70 yrs.	35	6	
		22.3%	18.2%	
Total		157	33	
		100.0%	100.0%	

or chronic urinary retention.[21] These obstructive symptoms can be translated by the patient via the IPSS score.[22]

In our study, the mean duration of urethral catheter removal is 10.7 hrs/min and theses result are in accordance with the prospective study conducted by Cheuk Fam Shum et al on 200 patients undergoing TUR-P, reported that 156 patients (78%) had successful outcome after catheter removal on the first postoperative day.[13] Another study by J. Chander et al showed that the mean duration of catheterization was 6.54 hours. However, 10 patients required re-catherization. [3]

As per our current departmental practice, the duration of hospital stay is five days or 120 hours. In our study the hospital stay has significantly reduced to a mean on 26 hours. J. Chander et al demonstrated in his study that by earlier catheter removal, duration of hospital stay had reduced from 3.1 to 1.28 days. [3] Similar results were seen in the study by Cheuk Fam Shum et al in which overall hospital stay was 1.6 days. [13]

The post TUR-P, post catheter removal, IPSS in our study is severe. The mean IPSS was 34.69 ± 1.34 with a p-value of 0.710. Comparing with the study of Bae WJ et al, their mean IPSS was 21.45 ± 0.54 [23]; it is believed that severe IPSS was because of the severe dysuria felt by the patient in their earlier voids. Despite an improved caliber of urinary stream the patient felt hesitant to void post early catheter removal.

In our study; successful outcome was seen in 157 patients (82.6%), while failed outcome was seen in 33 patients (17.4%). This result is favorable towards our attempt of early catheter removal after TUR-P in selected patients. J. Chander et al show similar results in which 98% of their 64 patients were discharged within 23 hours. They concluded that TUR-P could be safely conducted as a day care surgery. [3] However, their population was 64 patients while our study had a larger cohort of 190 patients.

Cheuk Fan Shum et al concluded in their study of 40 patients, that catheter free first postoperative day discharge was safe. However this study had a small population of 40 patients and their energy source for TUR-P was bi-polar while we used mono-polar.[13]

Okeke LI in his study day care transurethral prostatectomy in Nigeria[15] evaluated 180 patients after TUR-P and did not insert a urethral catheter post operatively. They concluded that TUR-P is a safe procedure to be conducted as a day case surgery. However choose to keep the patient on catheter irrigation in the immediate postoperative period in lieu of good and safe surgical practice.

The study by Prasopsuk S. et al also favors our findings towards early catheter removal after TUR-P.[12] Despite a result that is favorable to our attempt to decrease hospital stay while maintaining good practice standards and safety of our patients, our study has some limitations. Long term follow up in term of IPSS and uroflowmetry is lacking. This is because our patients are financially strained and arrive at our center after travelling long distances from their homes, hence frequent follow up becomes unaffordable for most of the patients. Uroflowmetry is a qualitative adjunct that adds to the value of IPSS, we could not perform as we did not

have a uroflowmeter, and provision by the government is awaited. Screening patients for their pre-operative PSA value to rule out suspicion towards carcinoma of the prostate is not performed in this study as it was not part of our departmental protocol to screen all patients. Only those with symptoms and clinically hard prostate on digital rectal examination were screened.

CONCLUSION:

In selected patients TUR-P can be performed with shorter hospital stay with minimal postoperative complications. This effort will help us to reduce, the patient waiting time to TUR-P, the complications associated with prolonged catherization and reduce the expense per patient.

Authors Contribution:
H. Mazahir Zulfiqar: Primary for data collection and writing
Sajjad Ahmed: Data Collection
Zein Ul Ameer: Primary Surgeon
M. Afzal Farroqui: Consultation and Guidance towards objective

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Orginal Article

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Comparison of Early Versus Delayed Showering on Post-Operative Wound Infections

Salman Habib Abbasi, Abdul Basit, Muhammad Farooq, Fazal Hussain Shah

ABSTRACT

Objectives: To compare frequency of SSIs with and without early showering after clean and clean contaminated surgical wounds.

Study Design and Setting: Randomized controlled trial was conducted at Department of Surgery. HIT Hospital, Taxila from June 2020 to December 2020.

Methodology: A total of 130 participants were recruited after taking informed consent. After clean and clean-contaminated surgery, first group was subjected to early showering (48 hours after surgery) while second group was not allowed showering until removal of stiches. Both groups were compared in terms of SSIs. Data was entered into SPSS version 25. The mean and standard deviation were used for the expression of continuous variables while frequency and proportion were used for qualitative variables. Both groups were compared by independent sample t test and chi square test. A p value of <0.05 was considered statistically significant.

Results: The mean age of the patients was 39.92 ± 11.42 years and there was male gender dominancy i.e. 74 (56.9%) were males while 56 (43.1%) were females. Clean surgeries were 81 (62.3%) and clean-contaminated proportion was 49 (37.7%). Collectively, 12 (9.2%) patients developed SSIs during clinical followup. There was no difference between groups in terms of age, gender, and wound types (p values 0.680, 0.157 and 0.587 respectively). In shower group, 3 (4.6%) and in non-shower group, 9 (13.8%) patients developed SSIs (p value 0.069).

Conclusion: Early postoperative showering can be implemented safely in clean and clean contaminated surgical wounds to minimize SSIs. The results should be evaluated in large RCTs.

Key words: Clean and contaminated surgeries, Surgical site infection, Postoperative bath.

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INTRODUCTION:

In lifetime, many people undergo various surgical procedures which result in surgical wound. After surgery, skin is closed with sutures, staples or adhesive tapes and glues which is covered by sterile gauze and adhesive tapes. The wound management after any surgery is continuous ongoing debate and every institution has its own protocols to prevent wound complications. The prevalence of healthcare associated infections (HCAIs) is more than 6% in developed countries and surgical site infections (SSIs) are third most common category. The bundled approach is required to combat these preventable infections. The dressing is done in sterile operation theatre environment. These protocols are followed to reduce surgical site infections (SSIs) which are one of the most common form of morbidity after any type of surgery.[1, 2] SSIs are associated with over a third of postoperative deaths. The spectrum of SSIs ranges from minor wound discharge, short-lived wound infection to life threatening situations like major abdominal, thoracic wounds dehiscence, septicemia. The SSIs increase the healthcare related costs, reduction in quality of life, poor psychological wellbeing etc. It is estimated that over one third of postoperative deaths are attributed to SSIs. To prevent SSIs, every hospital follows optimum sterilization protocols in all surgical categories. The traditional management of surgical wounds involves wound cleansing, dressing, and keeping wound dry until removal of stiches or staples.[3, 4]

To minimize the risk of SSIs, various measures are taken at each step of surgical management. Preoperatively, showers with antibacterial solutions or soaps can reduce the incidence

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of SSIs. Appropriate antibiotic prophylaxis with the aim of getting maximum serum concentrations at the time of surgery is recommended in almost all types of surgeries. Skin preparation with antiseptic solutions, preferably with alcohol based is an important step in operating room. During surgery prevention of hyperglycemia and hypothermia can decrease the incidence of SSIs. After surgery the optimization of lung functions and oxygen carrying capacity of blood is helpful in combating the various pathogens responsible for contagious complications.[5] Even though these recommendations are circulated in almost all healthcare centers but evaluation regarding compliance is somewhat not up to the mark. The breaches in the infection control procedures can lead to significant increase in SSIs. Every center report difference stats of infectious complications due to various factors ranging from variable implication of infection control measures and diversity in the surgical cases.[6]

There is considerable controversy in the literature regarding impact of early showering on SSIs. Some studies advocate the wound clearing or showering with tap water or saline after 48 hours to reduce to local colonization of microorganisms.[4] The National Institute for Health & Care Excellence (NICE) 2008 also recommended that showering after 48 hours in the postoperative period is safe. Both saline and tap water are equally effective and the wound infection rates are comparable.[4,7,8] The showering removes dirt, sweat and debris which provides favorable environment for the wound healing. Moreover, patient's satisfaction is also increased with early showering. Some studies showed the decrease in wound pain after early showering and reduction in SSIs.[5, 9] A recent literature review showed that early showering does not cause the increase in frequency of SSIs or other wound complications.[6]

In our study, we focused on whether the frequency of SSIs in influenced by early showering after clean and clean-contaminated surgeries. Literature has controversy at both local and international data bases. Water forbidden strategy after surgery can be challenged against early water contact strategy but the many surgeons are hesitant to some extent.[7, 10] The results would help us to evaluate the role of early showering on frequency of SSIs which would results in better management of surgical wounds.

METHODOLOGY:

This randomized controlled trial was conducted in Department of Surgery. HIT Hospital, Taxila from June 2020 to December 2020. The research was approved by local independent institutional ethical review committee vide letter no. ERC/19/13(b), dated 15 December 2019. One hundred and thirty patients undergoing surgical procedure resulting in clean and clean-contaminated wound were selected for this study. Informed written consent was obtained from all patients. All the patients with age range of 20 to 60 years, from either gender undergoing general (open appendicectomy, hernia repairs) and orthopedic surgeries (all extremity surgeries) were included. All the patients with chronic wounds, burn wounds, contaminated or dirty wounds and wound having drains for more than 48 hours were excluded. Also, patients with chronic liver or renal insufficiencies, diabetes, immunosuppression, pregnancy, or lactating were excluded. The patients underwent surgical procedures as per hospital protocols including pre and postoperative broad-spectrum antibiotics. After surgery, sterile gauze dressing with adhesive tapes was done in operation theatre. The randomization with ratio of 1:1 was done by computer generated random numbers. In group A, the surgical dressing was removed after 48 hours and patients were instructed to have tap water showering without rubbing or vigorous rinsing of the wounds. After showering wound was cleaned with saline swab and left open until stiches removal. In group B, the dressing of the wound was changed after every 24 to 48 hours until stiches removal without any permission to wound contact with water. The patients were discharged from the hospital as per standard protocols and advised for followup after 7 to 10 days. At the time of stiches removal, wound was examined for SSI (local redness, swelling and purulent discharge).

All the data was entered into SPSS version 25 registered for Microsoft windows. The mean and standard deviation were used for the expression of continuous variables while frequency and proportion were used for qualitative variables. Both groups were compared in terms of qualitative and quantitative variables including SSIs by independent sample t test and chi square test. P-value of <0.05 was considered as statistically significant.

RESULTS:

Total n=143 patients were recruited for study during the entire process. Out of which 9 lost follow up and 4 had to undergo second surgery due to complications. Total n=130 patients were divided into two equal groups. The mean age of the patients was 39.92 ± 11.42 years and there was male gender dominancy i.e. 74 (56.9%) were males while 56 (43.1%) were females. Clean surgeries were 81 (62.3%) and clean-contaminated proportion was 49 (37.7%). Collectively, 13 (9.2%) patients developed SSIs during clinical followup.

There was no difference between groups in terms of age, gender, and wound types (p values 0.680, 0.157 and 0.587 respectively). In group A, n=3 (4.6%) and in group B, n=9 (13.8%) patients developed SSIs (p value 0.069).

DISCUSSION:

Showering is considered a good hygiene practice for humans which has been associated with various positive healthy effects.[8] Showering before surgery is considered beneficial due to potential decrease in bacterial colony counts.[9] After surgery water contact with wound has been traditionally associated with increased frequency of wound complications but the research area has been debatable among surgeons.

Table 1. Demographic data among groups

Variable	Group A (Shower) (n=65)	Group B (Non-shower) (n=65)	P value
Age (years)	39.51 ± 11.75	40.34 ± 11.15	0.680*
Gender (M/F)	41/24	33/32	0.157†
Type of surgery (clean/clean-contaminated)	39/26	42/23	0.587†

* Independent sample t test
†Chi square test

Table 2. Frequency of SSIs among groups

SSIs	Group A (Shower) (n=65)	Group B (Non-shower) (n=65)	P value
Yes	03 (4.6%)	09 (13.8%)	
No	62 (95.4%)	56 (86.2%)	0.069†
Total	65 (100%)	65 (100%)	

†Chi square test

After 48 hours when wound is considered sealed due to early epithelization, the showering may be considered safe.[1,3]

Hsieh, P. Y., et al. (2016) compared early showering and non-showering groups in terms of various wound parameters in clean and clean-contaminated surgeries. This study randomized 222 patients and found that shower group had 1.8% while non-shower group had 2.7% SSIs (p value 0.751).[4] This study included various wound parameters including size of wound, site, postoperative pain, patient's satisfaction which were lacking in our data. In our study, these frequencies were 4.6% versus 13.8% for shower and non-shower groups respectively (p value 0.069). Another study on total knee arthroplasty (TKA) showed that bacterial colony counts are similar after early or latte showering (p value 0.28) but early showering had higher patient's satisfaction.[10]

Similarly, a study by Feilmeier, M., et al. (2014) showed that frequency of SSIs after clean surgeries of foot and ankle is 4.5% which remained unaltered by early or late showering.[2] A recent study by Jayathilake, A., et al. (2020) showed that showering just 24 hours after surgery can reduce the infectious complications significantly in clean and clean-contaminated cases. They concluded that to optimize the outcomes, surgical wounds should be kept moist, clean and patients should be advised early moblisation.[11] Another recent study favored early showering in patients after coronary artery bypass graft surgery. This study had the evidence that the rate of sternal wound infections was lower is shower group as compared to non-shower group i.e. 7.7% versus 32% (p value 0.038).[5]

Various systemic reviews showed that early or late showering does not influence frequency of SSIs after clean and clean contaminated surgeries.[3, 6, 7, 12, 13] All reviews concluded that due to wide confidence interval it is difficult to label early showering harmful or beneficial in terms of wound complications. Further randomized controlled trials should be done to dig out the facts. Showering is not recommended for all types of wounds. The clean and clean contaminated wounds should be considered for early showering but rest of the wounds should be individually assessed for showering.[1, 6]

Majority of the research data shows positive or neutral role of early showering on incidence of SSIs, but some studies warned the use of tap water for showing due to various pathogenic contaminations which may colonize the surgical sites like mycobacterium chelonae, pseudomonas.[14, 15] A recent Japanese study warned that showering has emerged as independent factor causing Mycobacterium avium complex lung disease (adjusted odds ratio 5.72, 95%, CI 1.99 to 16.46).[16]

The concept of showering before surgery reduces the frequency of SSI.[17] Both simple showering or showering with chlorhexidine solution are effective.[18] In many centres of the world it has become integeral part of preoperative care in high profile surgeries like onco surgery, coronary by pass etc.[19, 20]

CONCLUSION:

Early postoperative showering can be implemented safely in clean and clean contaminated surgical wounds to minimize SSIs. The results should be evaluated in large randomized controlled trials as early showering was beneficial in reducing SSIs, but results were not statistically significant.

Authors Contribution:
Salman Habib Abbasi: Conception and design, Critical revision for important intellectual content, final approval, and guarantor
Abdul Basit: Collection and assembly of data
Muhammad Farooq: Analysis and interpretation of data
Fazal Hussain Shah: Statistical

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Review Article

Open Access

Characteristic Features of SARS CoV-2

Shaista Bakhat, Yasmeen Taj

ABSTRACT

Corona-virus arose from China, spread globally and has become a great challenge for health care workers and Governments of several countries. This virus is transmitted predominately through respiratory droplets by symptomatic and asymptomatic carriers. The disease manifests itself with fever, dry cough and shortness of breath, these symptoms may be mild or have fatal outcomes. This virus attaches to the angiotensin converting enzyme (ACE) receptor, in the lung. This assessment, recapitulates the existing awareness of host features and the paths that are activated with HCOV (Human Corona virus) infection highlighting the infection derived stress response, autophagy, apoptosis and natural defense mechanism. The interaction of virulence tactics utilized by HCOV is also reviewed. This virus can be detected in the laboratory with help of reverse transcription polymerase chain reaction (RT-PCR), with up to 50%-69% false negative results. Treatment agenda is supportive therapy including supplemental oxygen, antipyretic, dexamethasone and ventilators.

Key words: Asymptomatic carrier, Corona virus, HCOV, RT-PCR

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INTRODUCTION:

Viral diseases continue to evolve with fatal outcomes. According to WHO[1] in the last twenty years many disasters like severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome corona virus (MERS CoV) have been recorded. In 2019, COVID-19 was first identified in a patient with pneumonia like symptoms from China in the city of Wuhan.[2] Later on cases like these (n=29) were labeled as "pneumonia of unknown etiology" and later known as novel Coronavirus. In month of Feb 2020, WHO declared it as COVID-19, stands for novel coronavirus infection disease-19.[3] Upto March 2020, SARS CoV-2 had amplified 13times and WHO gave it the status of a pandemic. It is named as SARS-CoV because of genetic resemblance with SARS CoV. World over, cases of SARS CoV-2 have multiplied and mortality and morbidity rate is high.[4]

METHODOLOGY:

This review article is searched through PubMed, Google, and Google Scholar engine with several key words related to Covid-19 structure, pathophysiology, prevalence, detection and therapeutic options. Articles were selected from 2001-2021. Searched is done by reviewing 200 original and review articles. Out of it, 100 were short listed.

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STRUCTURE:

Coronavirus belongs to Coronaviridae family in the order of Nidovirales. This virus is spherical single stranded, positive-sense RNA enveloped virus, covered with glycoprotein. The surface is decked with club spike like projections constituted of glucoprotein. These projections have the appearance of a solar corona, hence the name corona virus. Coronaviruses are composed of four structural proteins; Spike (S), membrane (M), envelops (E) and nucleocapsid (N). Spike protein consists of two functional subunits; S1 has a role in attachment with the receptor of the host and S2 causes the fusion of the viral envelops with the cell membrane of the host.SARS-CoV-2 has a protein furin which plays a vital function in replication and pathogenesis. There are four sub-types alpha, beta, gamma and delta with numerous serotypes.[5] The replicase genes of SARS CoV-2encodes two polyproteins, pp1a and pp1ab, these polyproteins are essential for replication and transcription.[6, 7]

REPLICATION CYCLE

Coronavirus replication cycle constitutes fusion and entry into the host cell, genome transcription and replication, translation of structural proteins, assembly, and release of new viral particle.[8] SARS CoV-2 attaches to host receptors ACE2 on epithelial lining cells of bronchial tract and pneumocytes lining the lungs with the help of viral spike (S), which is activated by type 2 trans-membrane serine proteases (TMPRSS2), within the host cell. The virus gains entry through endocytosis or membrane fusion, later it enters the nucleus where it replicates, mRNA, transcribes and new virion particles are made and released by exocytosis.

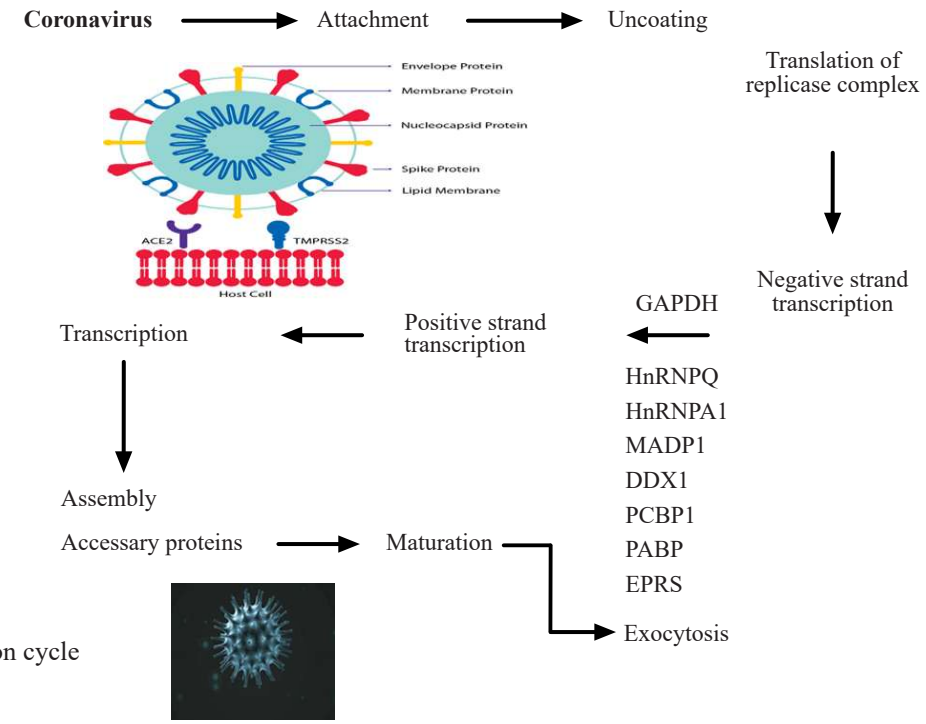

Fig 1: Replication cycle

PATHOPHYSIOLOGY:

According to gene ontology (GO) enrichment analysis, presence of ACE2 receptors on the epithelial cell lining the alveolar cells indicates increased activation of viral multiplication linked genes. These are the regulatory genes for viral life cycle. SARS CoV2 down regulates ACE2 signaling and responsible for inflammation, vasoconstriction and fibrosis. In later stages of infection, this virus can provoke excessive immune reaction, which is known as cytokine storm. The damage to the lung is linked with an inflammatory response and thrombosis in the micro vessels in the lungs. Autopsy studies have demonstrated that alveolar walls are diffusely thickened with mononuclear cells and macrophages infiltration. As a result interstitial mononuclear inflammatory infiltrates and edema occurred. Pulmonary edema along with hyaline membrane formation leads to acute respiratory distress syndrome. In critical cases, fulminant activation of intravascular coagulation takes place, resulting thrombosis in deep veins, embolism in the lungs, and systemic thrombotic response syndrome.[9]

In the universal GenBank researches from all over the world have deposited, analyzed and known to the public several gene sequences of SARS CoV-2.This gene recording is of primary significance in tracing the origin and phylogenetic tree of virus andmost importantly identification of different mutated strains. According to the latest research a mutation in the spike protein occurred in late Nov 2019 prompting it to jump to humans. One study related the pathogenic SARS CoV-2 gene sequence with that of the non-pathogenic SARS CoV. They studied the trans-membrane helical protein in envelop protein and found that location 723has a serine residue instead of glycine residue while the 1010 location has a proline instead of isoleucine. Viral mutate ion is the fundamental key for making it virulent allowing it to cause severe disease relapses.[10]

VARIANTS OF CORONA VIRUS

Scientists have classified coronavirus into 4 sub-groupings, known as alpha, beta, gamma and delta.

a. Alpha—229E, NL63
b. Beta—OC43, HKU1, MERS-CoV, SARS CoV
c. Gamma
d. Delta

Coronavirus variants found in United Kingdom (B.1.1.7), Brazil (P.1) and South Africa (B.1.35 share some mutations with B.1.1.7).[11]

TRANSMISSION

The coronavirus infections most commonly spread via droplets throughout face to face exposure while a person is talking, coughing and sneezing. Contact to a person who has infection within a distance of six feet and a time limit of 15 minutes is also associated with risk of high transmission. Short contact with asymptomatic carriers is less of a risk. Contact touching is also a role.[12] Vertical transmission for maternal SARS CoV-2 is associated with low risk and no maternal deaths or unfavorable neonatal outcomes.[13] The clinical importance of SARS CoV-2 infectivity from nonliving objects depends on the viral load which appears to be high on porous surfaces like stainless steel and plastics.[14]Virus has been isolated from hospital surfaces for up to 3-4days,

Table 1: Events in pandemic of Coronavirus[17, 18]

Dec 2019	Jan 2020	Feb 2020	Mar 2020	April 2020	May 2020	June 2020	July 2020	Aug2020
Dec 31: China informs WHO about cluster cases of pneumonia with unknown etiology	Jan 7:WHO officially announce a new coronavirus named 2019-nCoV	Feb 2: first death of Chinese outside in Philippines	Mar 11: WHO declares it as pandemic	April 1: cases of COVID-19 goes beyond 1 million	May 9: global cases surpasses 4 million	June 29: global cases go above 10 million	July 31: 17106007 reported cases and 668910 deaths globally	Aug 31: 25 million cases and 800000 deaths globally
	Jan 13: in Thailand first confirmed case outside the China	Feb 11: WHO declared it as COVID-19	Mar 16: cases outside china are increased	April 9: cases in Italy more than 132000	May 22: in Brazil 330000 cases			
	Jan 30: WHO proclaims coronavirus a global emergency as coronavirus cases detected in Australia, US, Nepal, Japan, France, Singapore, Malaysia, Taiwan, South Korea and Vietnam.	Feb 14: first case reported in Egypt and f death of first case was reported in France	Mar 18: WHO publicizes the International Solidarity Trial	April 28: cases in US exceeds 1 million with 58000 deaths				

Sep 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2021
Sep 7: 27million reported cases and 900000 deaths globally	Oct 5: 34.8 million morbidity and over 1 million mortality rate globally	Nov 3: 46 million reported cases and 1.2 million mortality rate globally	Dec 1st week: 61.8 million reported cases and 1.4 million deaths globally	Jan 5: 83 million reported cases and over 1.8 million mortality rate globally
Sep 28: 32.7 million reported cases and 991000 deaths globally	Oct 20:over 40 million reported cases and 1.1 million mortality rate globally	Nov 10: 49.7 million reported cases and 0ver 1.2 million mortality rate globally	Dec 22: 75 million reported cases and 1.6 million mortality rate globally	Jan 12: 88 million reported cases and over 1.9 million mortality rate globally
		Nov 17: 53.7 million reported cases and 1.3 million mortality rate globally	Dec 29: 79 million reported cases and over 1.7 million mortality rate globally	

although it can disintegrate within 48-72hours.This emphasizes the need for adequate environmental and hand sanitization strategy.[15] viral particles in the oral and nasal passages attain the significant levels at the time of beginning of symptoms and viral discharge occurs 2-3 days before the onset of symptoms. Although PCR test shows a presence of detectable nucleic acids in throat swabs, six weeks after the commencement of symptoms, reports show that viral cultures do not show any growth a week after onset of symptom. Therefore it can be recommended that infected individuals can be unconfined from quarantine on the improvement of clinical symptoms. CDC (the center for disease control) recommends isolation for at least 10days after onset of symptoms and 3days after improvement of symptoms.[16]

Patients with clinical evidence of SARS CoV-2 may be tested by RT-PCR which is a quantitative test for detection of viral nucleic acid. The samples are obtained from nasopharyngeal swab, sputum and lower respiratory tract aspirates or wash.[20]This is the gold standard method for isolation of viral infections, as it is simple, quick and reliable method. Major disadvantage with the real-time RT-PCR test is the hazard of acquiring false-positive and false-

Table 2: Prevalence of SARS CoV-2 in Pakistan[19]

Feb 2020	March 2020	April 2020	May 2020	Jan 2021
Feb 26: 1st case of Coronavirus detected in student at University of Karachi 2nd case from Federal Territory Both returned from Iran	March 2: 5th case reported from Federal area	April 1: 2291 cases were reported	May 29: 900 children under age of 10 had tested positive	Confirmed cases-519,291 Deaths-10.951 Recovered-473,639
	March 8: 7th case reported in Karachi	April 2: 2450 cases		
	March 10: 1st case in Quetta	April 3: 2708 cases		
	March 11-19: 30-80 in Punjab 23-81 in Baluchistan	April 5: 3000 cases		
	March 20: 1st death was reported in Sindh	April 7: 4005 cases		
	March 22: 3rd death in Khyber Pakhtunkhwa	April 11: 5000 cases		
	March 29: 1526 cases were reported	April 22: 10,000 cases		
	March 30: 1865 cases were reported			

Table 3: Comparison of RT-PCR Test and Ag-RDT[23]

Features	RT-PCR Test	Ag-RDT
Target	Viral RNA	Viral antigens
Specimen type	Nasopharyngeal and oral swabs	Nasopharyngeal swab
Sensitivity	High	Moderate More false negative
Specificity	High	High
Test complexity	Complex	Easy to use
Lab settings	Highly sophisticated lab settings	May be outside conventional lab settings
Cost effectiveness	Expensive	Low cost

negative results. Therefore a result which is negative does not mean that SARS CoV-2is not present and should not be used as the only guide for management and treatment presenting the symptoms. The diagnostic test like real-time RT-PCR and clinical presentations are the guidelines for management of this pandemic.[21]

SARS-CoV-2 can also be assessed by serological testing. These tests can evaluate previous encounter with the virus but are not helpful in making any diagnosis of current infection. Drawback of serology is cross reactivity with other Corona virus. This test is enzyme-linked immunosorbent assay (ELISA)-based and useful in detecting IgM and IgG antibodies in serum, plasma and whole blood. This test was developed by CDC to find out how many people in the US have already been exposed to this virus. This test utilizes SARS-CoV-2 S protein as antigen rather than live virus. This test was designed by the center for vaccine development for research at the institute of National Health. This test has specificity more than 99% and a sensitivity of 96%. CDC utilizes this test for surveillance purpose.[22]

Another serological test used as Rapid antigen testing (Ag-RDT) in which antigen is nucleocapsid protein (N) within the core of SARS-CoV-2.This protein is irregularly expressed in infected cells. The test has specificity of 98.5% and sensitivity of 84.1%. This test does not have disadvantage of cross reactivity and can generate result within 10-30

minutes at low cost.

Ultrasonography also plays an important role in guiding the treatment of patients. LUS (lung ultrasound) helps to evaluate cardiorespiratory failure.[24]

Chest CT scanning in SARS CoV-2 associated pneumonia shows ground-glass opacification and consolidation. Some studies have showed that abnormalities on chest CT scans are usually bilateral with Pleural effusion, pleural thickening, and lymphadenopathy.[25]

Support tests are CBC (complete blood count), C reactive protein, D dimer which is increased in patients with acute venous thromboembolism).[26]

THERAPEUTIC OPTIONS

There are no specific therapeutic options for SARS CoV-2. Physicians deal it with supportive and oxygen therapy.

In acute respiratory distress syndrome, when SpO2 (oxygen saturation) =93-94%, respiratory rate more than 28-30/min, or dyspnea then 40% oxygen should be provided. Patient should be reassessed first within 5-10 minutes then after 6 hours, if there is no improvement; the physician has to go for non-invasive treatment.

HNFO (high nasal flow oxygen) has a great risk of aerosolization, so it should be given within a negative pressure room. In this procedure oxygen is provided 30-40L/min, FiO2 (fraction of inspired oxygen) 50-60%. At this level, if symptoms are still not improved then therapy is switched to NIV (noninvasive ventilation). It is done with positive pressure. It has a vital role in treating SARS CoV-2 associated respiratory failure.[27]It is recommended to put antimicrobial filter at expiratory valve. Ventilation with pressure support begin with positive end expiratory pressure (PEEP) at a pressure of 5 cmH2O examining the easiness, if the patient is comfortable and bring the pressure to 8-10 cmH2O, FiO2 (fraction of expired oxygen) 60%.[28]If there is still marked deterioration, intubation is required. If the patient presents with marked negative intrathoracic pressure to sustain minute ventilation, we use a bag method with a PEEP valve to make a patients ready for ventilation immediately after the intubation process. If this method is to be employed a HEPA (high efficiency particulate air) filter must be positioned between the endotracheal tube and the bag.[29]

Therapeutic guidelines includes the use of systemic corticosteroids for management of acute respiratory distress syndrome (ARDS) due to other etiological reason are not suggested but in severe CARDS (SARS CoV-2 associated acute respiratory distress syndrome) these medications are commonly utilized(e.g., methylprednisolone 1 mg/Kg/day). A current large-scale trial RCT (the RECOVERY trial) confirmed the use of steroid dexamethasone decreases deaths by one-third.[30]

Though antiviral therapy has not been effective against SARS CoV-2, many proposals have been tried like such as the use of antiviral drug lopinavir/ritonavir (400/100 mg which is given by mouth twice a day). But later on, randomized controlled studies also showed no beneficial effects.[31] The remdesivir drug is an inhibitor of RNA polymerase against RNA viruses and effective as recommended preclinical studies.[32]

Chloroquine (500 mg twice a day), and hydroxychloroquine (200 mg twice a day) were also suggested for treating the SARS CoV-2 infection and non-randomized study showed that it has adjuvant activity with macrolide and azithromycin. These drugs can inhibit the entry, uncoating and even entire replication cycle.[33]

An experimental trial in clinics has been commenced in June 11, 2020 for exploring a cocktail of antibody for the management of COVID-19 patients. In this process antibodies were received from recovered person and injected to diseased person.[34]

Patient with SARS CoV-2 also face complications like coagulopathy majorly responsible for pulmonary microvasculature thrombosis and systemic thromboembolism. In this scenario anticoagulopathy as (e.g., enoxaparin 1 mg/kg after every twelve hours) is recommended in non-hemophilic patients.So there is requirement of tailoring the clinical status of each patient.[35]

VACCINATION

a. Pfizer-BioNTech (UK)[36]
b. Johnson and Johnson/Janssen (America)[37]
c. Sinovac[38] (China)
d. Sputnik[39] (Russia)
e. Moderna[40] (America)
f. Covaxin (India)
g. Paksino (Pakistan)

CONCLUSION

As of March 2021, there have been reported 121 million people who have suffered and more than 2.67 million people have died. From a pragmatic point of view studies on HCOV interactivity and linkage is imperative in the possibility of future potential pandemics from occurring and the resurfacing of previously nonpathogenic infections as highly virulent diseases. A better appreciation of HCOV host interactivity will further allow us to pin point essential crucial factors that mastermind the mechanism of infection and institute treatment strategies. Chemotherapeutic options have shown to be less expected to select for drug resistance HCOV types. These along with boosting immunity by a vast scale vaccination campaign may be beneficial in this war. Ultimately such studies on the host and viral factors may be beneficial in extrapolating to other zoonotic diseases making us more aware on policies to prevent the discrimination of these pathogens. DNA mRNA vaccines offer huge advantage over the traditional type of vaccines since they only use genetic code from a pathogen. The hope

that gene based vaccines will one day provide a vaccine for malaria, HIV, cancers or ready to stop next pandemic or no longer fetched.

Authors Contribution:
Shaista Bakhat: Original idea, Literature search, Manuscript write up, data collection, final lay out
Yasmeen Taj: Literature search, critical review, proof reading

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Case Report

Open Access

Intussusception Presenting as Rectal Prolapse

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ABSTRACT:

Intussusception is the invagination of a segment of the intestine into the lumen of the distal or proximal segment. It is one of the commonest causes of intestinal obstruction in the toddlers. Ileo-colic intussusception is the most common type. At times the inussusceptum may protrude through the anal canal and mimic a rectal prolapse. The diagnosis may be delayed in such cases leading to increase morbidity as well as mortality. Therefore, a high index of suspicion is required in such cases. In this case where a colo-colic intussusception presented like rectal prolapse. Emergency surgical reduction was carried out under general anaesthesia and the baby had a smooth recovery.

Keywords: Anal canal, Intussusception, Intestine, Prolapse.

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INTRODUCTION:

Intussusception is defined as the invagination of a segment of the intestine into the lumen of the distal or proximal segment. The invaginating loop is known as intussusceptum and the receiving part is called intussuscepiens. Intussusception is the most common cause of acute intestinal obstruction in children under 2 years of age.[1] Children present usually with the classical signs of small bowel obstruction (SBO). Bilious vomiting, abdominal distension, and severe colicky pain abdomen is accompanied by red currant jelly stools and palpable mass in the lower abdomen. At times the invaginating loop may protrude through the anal canal and present as a prolapsed rectum. In one case series its prevalence has been claimed to be 29% of all the cases.[2] A high index of suspicion is required in such cases as prompt management is required in order to avoid ischaemic injury to the involved loop of intestine. Here we present a similar case of a baby girl who presented with a mass protruding through the anus.

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CASE REPORT:

A three years old baby girl presented to the emergency department in the evening with history of severe colicky pain in the abdomen and anorexia since morning. She developed a mass protruding through the anus in afternoon which gradually increased in length. She was also passing mucus and blood in stools. On examination she was irritable and crying with pain. An almost 15 cm long mass was coming out of anus (Figure.1). Her pulse rate was 120/min. She looked pale and was afebrile. She had guarding and tenderness in her lower abdomen however, no mass was palpable. A finger could be easily passed between the two loops of the protruding gut and anal canal. Her blood complete counts and electrolytes were normal. Ultrasound of the abdomen was suggestive of "target sign" with central echogenic and peripheral hypoechoic portion of gut in the pelvis. Longitudinal scan showed "pseudo-kidney sign". On colour doppler blood flow was present in both loops, suggesting colo-colic intussusception. She was admitted and prepared for emergency laparotomy. Under general

Figure.1 Intussusception protruding through anus mimicking rectal prolapse

Figure.2: Last part of intussusception being reduced easily

anaesthesia the intussusception was kept in hot saline packs for 10 minutes and then reduction was tried through anus but could not be reduced. A lower transverse incision was made and the intussusception was reduced easily (Figure.2). She made an uneventful recovery and was discharged on second post-operative day.

DISCUSSION:

Intussusception is a well-known cause of intestinal obstruction in children. The exact aetiology is still unknown and almost 81% of the cases are idiopathic.[3] Various conditions have been found to be associated with it.[4] Adenovirus infection[5] as well as vaccination against rota virus have been proposed to increase the risk of intussusception.[6] It can occur at any age, but 80-90% of the cases are usually less than two years old.[7] Ileo-colic is the most common type but it is uncommon to prolapse through the anus. The colo-colic or sigmorectal is the relatively uncommon but likely to protrude through the anus as it was found in our case. Pathological lead point (PLP) may be present in 20% cases and mostly presenting in children more than one year of age. The age of patient in our case was 3 years however, there was no PLP. Patients present with signs of SBO. Vomiting is almost found in more than 80% cases. Our patient had nausea but no vomiting because the obstruction was distal and moreover, she presented early to the emergency department. Ultrasound of the abdomen is the investigation of choice with more sensitivity and high specificity.[8] Once there is prolapse of intussusception it can be easily diagnosed by insinuating finger between the anal canal and the intussusception to differentiate it from the rectal prolapse. In rectal prolapse a finger cannot be passed freely beyond anus between the prolapsing mucosa and the anal canal but it will easily go around the intussusception. Spontaneous resolution of the intussusception may occur in a few cases but most would require hydrostatic reduction or surgery. Recurrence is more in cases of hydrostatic reduction. Similarly, children older than one year, having vomiting and palpable mass were found to be at high risk of recurrence.[9]

A high index of suspicion is needed to diagnose children having protrusion of the intussusception through anus. These are the cases confused with rectal prolapse. Moreover, they do not present with the classical signs of the disease. Delayed treatment may lead to gangrene of the involved segment of the gut thus increasing the morbidity and mortality by many folds.[10]

CONCLUSION:

Both intussusception and rectal prolapse are common in toddlers. Rectal prolapse is usually managed conservatively. On the other hand intussusception if left untreated can lead to gangrene of the involved segment of intestine and has high mortality and morbidity. A high index of suspicion is needed to differentiate the two conditions and initiate prompt management.

Authors Contribution:
Asrar Ahmad: MOK Case
Irum Saleem: Literature
Mahwish Mahboob Bhutta: Write up
Mehwish Mughal: Referencing
Nisar Ahmad: Discussion

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Commentary Open Access

An Abridgement on Curcumin Potentials for Covid-19 Treatment- A Miracle Drug?

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The world was brought to a standstill by the rapid spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), responsible for COVID-19. Initially recognized in Wuhan, China, in December 2019, it was announced to be a pandemic. It is known to spread from person to person via respiratory droplets such as saliva, cough and sneeze. The infection can be established by the real-time reverse transcription-polymerase chain reaction (rRT-PCR) test on the mucosal swabs and by testing the IgG and IgM on the blood samples. Patients experiencing severe symptoms are advised to undergo computed tomography (CT) scans to rule out extensive lung involvement[1]

The pathophysiology of respiratory distress in SARS-CoV-2 is explained by the enveloped nature of the non-segmented positive-sense RNA virus that mainly expresses various proteins, primarily the S-protein. The S-protein interacts with ACE-2 receptors present in the alveolar cells of the lungs, nasal epithelium, intestinal lining, etc. [2,3] This interaction causes suppression of ACE-2 receptors, resulting in potential complications like pulmonary hypertension, acute lung injury, and lung fibrosis. While many are asymptomatic from the infection, a large spectrum of the patient population presents with fever, lethargy, headache, muscle pains, and diarrhoea. The respiratory viral infection even manifested as silent hypoxemia, respiratory distress, and multi-organ failure.[3]

Turmeric is extensively used in their authentic cuisine and conventional medicine. Curcumin, the primary yellow substance in turmeric, is effective against various pathogens and viruses like Hepatitis, Zika, and HIV. [4] Inflammation and oxidative stress have been the primary mechanism behind the pathophysiology of a wide variety of diseases. Few of the many diseases include alzheimer's disease, parkinson's disease, cancers, atherosclerosis, arthritis, psoriasis, bronchitis, asthma, allergies, whereas infections like acquired immunodeficiency syndrome (AIDS) and COVID-19.[8]

Curcumin is known to exhibit anti-inflammatory properties and may act as a potent agent to help fight against these diseases. The anti-inflammatory effect is mainly due to its ability to prevent the upregulation of cardinal inflammatory enzymes like cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS); these are responsible for the pathogenesis of many carcinomas and inflammatory diseases. [9] Another key agent involved in the pathogenesis of inflammation is tumor necrosis factor α (TNF-α). Its effect is controlled by regulating a transcription factor called nuclear factor (NF)-κB. (NF)-κB is triggered by various bacteria, viruses, stress, and other environmental factors like smoke. Curcumin may further help with suppressing inflammation by hindering the stimulation of (NF)-κB. Curcumin also has detrimental effects on free radicals such as reactive oxygen and nitrogen species (ROS, NS) which may favor in preventing oxidative stress.[8]

In the coronavirus case, curcumin suppresses ACE-2, which prevents the SARS-CoV-2 virus from targeting the cells. Moreover, the substance can stop the replication of RNA synthesis, demonstrating its antiviral properties. Few studies also suggested that it hampers the infection by binding to the molecular ligand instead of the viral proteins.[5] Some studies have shown that curcumin also decreases ovalbumin (OVA), responsible for hyper-reactive airway disorders and allergen-induced broncho-constriction. Curcumin also helps in gene expression alteration, which causes cell cycle arrest in patients with pulmonary fibrosis.[10] Curcumin has anti-inflammatory properties, which suppress NF-κB activity leading to a significant reduction in the pro-inflammatory cytokines.[2] Thus curcumin is beneficial in patients with chronic diseases.

Like other respiratory viruses, SARS-CoV-2 also expresses pro-inflammatory mediators, leading to the release of inflammatory cytokines causing increased vascular permeability, which can induce pulmonary edema and severe acute respiratory distress. The anti-inflammatory and immunomodulatory properties expressed by curcumin inhibit inflammatory mediators such as cytokines, potentially

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beneficial in COVID-19 patients. The anti-inflammatory property possessed by curcumin may also help in other inflammatory disorders like inflammatory bowel disease, arthritis, etc. [11] Curcumin promotes cardiovascular health. Curcumin effectively improvising the cardio toxicity caused by various medications such as doxorubicin and non-therapeutic agents. Curcumin reduces oxidative stress and inflammation in the cardiac tissues by regulating and suppressing various inflammasomes.[6]

Apart from the anti-inflammatory effect, Curcumin has shown other beneficial effects such as anti-thrombotic by lowering serum cholesterol, which might prevent atherosclerosis and metabolic syndrome and diabetes mellitus. Moreover, Curcumin has a possible role in the homeostasis of calcium $(Ca)^{2+,}$ which might be helpful in the prevention of ventricular arrhythmias. The anti-inflammatory effect also alleviates atrial arrhythmia. The inhibitory effect on the p300-HAT has shown improvement in animal models with cardiac failure and hypertrophic cardiac conditions.[7,8]

Furthermore, this significant component exhibits properties to relieve pain, abnormal body temperature, and fatigue which can be substantial in managing symptoms in patients with COVID-19.[3] COVID-19 also can induce venous thromboembolism in different ways. The proposed mechanisms behind thrombus formation are activation of coagulation pathway by the released cytokines, endothelial damage, which is identified by elevated levels of von willebrand factor, systemic inflammation caused by toll-like receptor factors, activation of pro-coagulation state, hypoxia-inducible transcription factor leading to thrombus formation in hypoxic conditions, and last but not the least anti phospholipid antibodies causing immune-mediated damage and thrombus formation. [12]

Curcumin exhibits anti-thrombotic and anticoagulant properties by prolonging activated partial thromboplastin time (aPTT) and prothrombin time (PT) and decreasing thrombin and FXa activity could demonstrate beneficial effects in patients with COVID-19 infection. [11,13]

Additionally, the inclusion of other known and available vitamins and trace elements such as vitamin C and zinc has shown beneficial effects in augmenting the body's natural defence mechanism against COVID-19. It has also helped in the post-infection phase for many.[2]

In a nutshell, Curcumin exhibits anti-inflammatory and anti-oxidant properties, making it a promising agent against many viruses and other inflammatory diseases. Thus, it had been a significant constituent of many traditional medicines throughout many parts of the world. Many studies have helped establish that the SARS-CoV-2 virus causes cytokine surge by activating different inflammatory mediators, leading to pathological conditions such as respiratory distress, pulmonary fibrosis, and even thrombus formation. Curcumin's anti-inflammatory effect may contribute at various levels to ameliorate the inflammation in the patients with COVID-19 infection, thus, acting as a potent adjuvant therapy in the treatment of COVID-19.

Authors Contribution:
Priyanka Anvekar: Construct the Manuscript, References and Detailing, Title
Manoj Kumar Menda: Proof Read, Plagiarism and Finesse
Petras Lohana: Title, Proof Read.

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Letter to Editor

Open Access

Covid-19 Vaccination and Immunization Barriers in Pakistan

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From January 2020 to May 2021, Pakistan quoted to World health Organization 858,026 confirmed cases and 18,915 deaths of COVID - 19. China donated Pakistan Sinopharm vaccines in February 2021, and the stagewise immunization program started with an enrolment of healthcare workers and the elderly at priority. A total of 2,894,861 vaccine doses have been administered as per statistics of the earlier half of May 2021, which is approximately only 3% of the total population and target for this year is 30%. [1] Several wild conspiracy theories sprouting throughout the community is fuelling the misleading narratives of vulnerable population of Pakistan leading to increased Skeptism against covid-19 vaccine .Of theses alleged claims of religious prohibitions plea that virus was an illusion against Islam to empower Jews and through vaccine nano chips will be inoculated in people to gain control through 5G towers.[2]

There is an upsurge of several cases and fear of disease due to the ongoing pandemic situation in India. This has forced the government to impose and heighten up virus spread prevention restrictions. The experience of the terrifying situation in India should have alarmed our authorities; they have failed to comply with the seriousness of the issue. Pakistan is on the 29th slot out of 30 countries that have conducted the greatest number of tests per million population (PMP), hence second last on enlistment with 39,136 tests carried out. Israel, United Kingdom and United States secured top 3 ranks with 1,273,050, 1,266,538 and 1,052,930 tests per million populations respectively. Even India has conducted around four times more tests.[3]

Significant vaccine hesitation also has an enormous impact on the control of disease and the emergence of new fatal strains among immunocompromised. Approximately 142,315 healthcare workers were registered in Sindh for Covid – 19 immunization programs, however, 33,356 refused inoculation. To discourage this attitude authority had to take major steps of job termination warning. The perspective of front-line warriors of disease who have seen patients dying in their hands and relatives in sheer agony, then the unwillingness of the general population with low literacy is not an unusual revelation.[4]

As evident in the literature by American publication Bloomberg about the global disproportion between the number of vaccines. Pakistan will require about 10 years to immunize 75% of its population, India would have the option to inoculate a similar level of its populace is around three years. United States, Britain, and Israel were probably going to arrive at the 75% objective inside a quarter of a year.[5]

Pakistan is already a hub of infectious diseases with epidemics like Tuberculosis and Hepatitis C, with the 6th and 2nd highest disease burden globally. The WHO notified, the rate, invasiveness, and mortality of Tuberculosis in Pakistan as 230 per 100 000, 310 per 100 000, and 39 per 100 000, respectively. This reflects 410 000 cases and 69 000 deaths of Tuberculosis each year in Pakistan. [6]

Pakistan Polio Eradication Programme (1994) in conjunction with support provided by WHO and UNICEF is determined to eradicate the crippling disease as Pakistan and Afghanistan are only two countries worldwide fighting with menace. In the mid-1990s, the yearly occurrence of polio was assessed at more than 20 000 cases every year. So far in 2020, 80 cases have been accounted all over the country from Punjab 13, Sindh 22, Khyber Pakhtunkhwa 22, and Baluchistan 23. [7] Pandemic of COVID illness 2019 has disrupted immunization programs globally, hence exalting perilous fatal vaccine-preventable diseases. Due to the COVID-19 outbreak vaccination campaigns halted in Pakistan therefore depriving, leading 40 million children of polio vaccination. Deferrals in polio inoculation probably will not have a prompt effect but, in the long haul, the expansion in polio cases in Pakistan could bring about worldwide dissemination of infections. [8] This is of momentous concern as we have already failed to convince the public to adhere to polio vaccination and disruption in the program can lead to wastage of enormous efforts already contributed towards the program. Additionally, if this scepticism for COVID – 19 vaccinations prevailed we will be stuck into Catch 22 for more epidemics and pandemics.

The advent of Coronavirus disease and vaccination prompted

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Flu vaccination disappearance from the market due to various reasons. Every year on the opinion of epidemiology and health experts to reduce mortality and morbidity high-risk individuals are encouraged to get an influenza vaccination. Two significant distributors are Sanofi and Abbot. Due to boycotts of French products on religious grounds and lack of provision from Abbot due to elevated demands from developed countries Pakistan has failed to procure influenza vaccination hence adding to the dilemma of diseases burden.[9]

A fully immunized child is conceived with at least 1 dose of Bacilli Calmette-Guérin, 3 doses of oral polio, DPT3, and measles1 vaccination, which ranges from 47% - 57% in Pakistan. Child mortality is characterized by 50% of the country's mortality rate compared with 8% globally impacted Pakistan due to failure of EPI implementation. However, under five years constitute only 15% of the total 'country's population [10] Efforts are in hand to eradicate polio, measles, and neonatal tetanus. Inadequate service delivery, which leads to irregular access and poor service utilization, was the key reason for this poor performance. Recognized issues leading to failure of the Expanded Program of Immunization (EPI) as per various studies conducted on the subject are distant EPI centers, sporadic access to centers, and deficiency of expert staff and services.[11] These reasons could also be hindrances to the Covid–19 vaccinations program as well.

Authors Contribution:
Sana Abbas: Conception and Draft
Beenish Abbas: Proofreading and research material

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