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Editorial

WASH STRATEGY TO IMPROVE PRACTICES OF WATER AND SANITATION IN HEALTH CARE SETTINGS.

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According to UNICEF, one out of every four health institutions worldwide does not have access to clean water.[1] The first comprehensive global assessment of water, sanitation, and hygiene (WASH) in health care institutions was conducted by the World Health Organization.[2] Access to safe drinking water and sanitation is a fundamental human right as well as a human requirement. Sustainable Development Goal 6 (Water and Sanitation) emphasizes the need for long-term access to safe drinking water and sanitation.[3] The World Health Organization has developed a water sanitation and hygiene plan that is intended to assist countries in defining national standards, enacting laws, and developing effective surveillance systems to achieve Sustainable Development Goal 6.[2] The most important components of WASH are the reduction of open defecation and the improvement of water quality. The implementation of WASH in schools and health institutions is critical because diarrhea and other health problems lead to absenteeism from school and, in certain cases, dropouts from high school or college. In health care institutions, hand washing and disinfection can help reduce the spread of infectious diseases and hospital-acquired ailments.[1]

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WASH strategy has the potential to inhibit the development of antibiotic resistance. WASH is critical in catastrophe situations because it can prevent infections such as typhoid. Preventing them becomes a critical intervention in the preservation of human life.

WASH is more than a requirement for good health; it also contributes to the overall well-being of individuals, their families, and entire communities when it comes to clean water and sanitation. Along with contributing to health concerns such as diarrhea, contaminated water pollutes ground and surface waters that are utilized for drinking, irrigation, bathing, and other domestic duties as well as for agricultural and industrial purposes. The upshot of this is a great deal of stress on the communities involved. Arsenic, fluoride, and nitrate poisoning of water continue to be a health danger, as does the presence of other chemicals in the water. If emerging contaminants such as micropollutants, medications, and microplastics in drinking water are not as damaging to human health as germs such as Legionella, public attention and scarce resources could be diverted away from more significant dangers. Trachoma, soil-transmitted helminths, and schistosomiasis are all preventable diseases that can be avoided with proper handwashing.[4] The mortality rate for newborns and mothers in Pakistan is relatively high. One of the most significant contributors is sepsis. Many healthcare facilities in Pakistan do not adhere to WASH

standards. According to a comprehensive review, water, sanitation, and hygiene (WASH) interventions reduce the risk of diarrhea in children aged 0–5 years by 27% to 53%.[5] The implementation of WASH programs in Pakistan has the potential to lower maternal and child death rates. During the COVID-19 pandemic, WASH efforts have made a significant contribution to the prevention of disease spread. The use of appropriate handwashing practices, in addition to social isolation and the wearing of a mask, will assist in reducing the transmission of the virus. Implementing WASH methods to prevent communicable diseases is critical, and health care providers play a critical role in this effort.[6] Through the development of a WASH strategic plan based on an overarching framework, it is possible to clarify the priorities of the WASH Programme, including new and developing functions. As a global framework, it has the flexibility to be customized to the individual needs and conditions of many different regions and nations. In health-care settings, the initial stage is to teach team members, who then travel to the health-care facility where WASH will be implemented. They then proceed to evaluate potential hazards associated with water and sanitation procedures in a healthcare context as a further step. Interviewing at a health center is another method of learning more about the practices of that particular health center. Risk mitigation recommendations are offered in the following phase. The next stage will be to put the plans into effect as soon as possible. Improved water and sanitation methods are the product of ongoing research and evaluation. Because of this, it is a risk-based strategy that focuses on high-risk areas while also assessing progress regularly to raise the overall standard of living.[2]

Maternal mortality, newborn mortality, and hospital-acquired infections are all higher in Pakistan than in the rest of the world. Water, sanitation, and hygiene (WASH) is an approach that helps prevent the spread of illnesses in hospital settings. The problem of hospital-acquired illnesses that are resistant to antibiotics is a worldwide public health concern. To improve the health of communities, it is desirable to prevent and reduce high-risk activities in healthcare settings. A reduction in hospital acquired infections in tertiary care hospital of Pakistan was observed when health care workers followed WASH practices.[7]

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Original Article

FACTORS ASSOCIATED WITH TERMINATION OF PREGNANCY AMONG MARRIED ADOLESCENT GIRLS IN PAKISTAN: SECONDARY ANALYSIS OF DATA FROM PAKISTAN DEMOGRAPHIC AND HEALTH SURVEY

Abida Tehreem[1], Rubeena Zakar[2], Bilal Saleem Khan[3], Mamouna Faqir Hussain[4], Rahat Afza[5]

ABSTRACT:

Background: Child marriage exposes girls to increased health problems and violence, denies them access to social networks and support systems, and perpetuates a cycle of poverty and gender inequality. Termination of pregnancies can be the consequence of teenage pregnancy. This study aims to find the association of factors in teenage mothers that lead to termination of pregnancy.

Material and Methods: The sample of 5694 women 10-17 years of age was selected from Pakistan Demographic and Health Survey (PDHS) 2012-2013.

Results: It was considered that women married as children had more risk of termination of pregnancy. Out of the total, 37% of women married as children experienced termination of pregnancy. A higher number of women married as children were poor, uneducated and living in rural areas. This indicates that child marriages are a huge concern for Pakistan and drastically increased risk of maternal morbidity and mortality.

Conclusion: Despite early age and social inequity other factors such as the experience of violence, blood relation with husband, few antenatal visits, low education level and employment status of women has a profound effect on termination of pregnancy.

Key Words: Maternal mortality, Reproductive health, Pregnancy

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INTRODUCTION

Termination of pregnancy has serious implications for women's health. It can be a stillbirth or miscarriage. World Health Organization defines stillbirth as a baby born with no signs of life at or after twenty-eight weeks' gestation. Miscarriage is the spontaneous termination of a pregnancy at an early stage before the embryo is capable of surviving outside the womb, and it is a common risk in a first pregnancy. Pregnancy loss can have various adverse effects on the physical and mental health of a woman.

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A spontaneous abortion is a trauma that affects the woman's basic belief system.[1] Woman who experiences termination of pregnancy or spontaneous abortion are likely to have depression and mental illness as well as may face difficulties to cope with further pregnancies including weak mother fetus bonding. Miscarriages may lead to future health-related complications such as anemia, infections, and difficulty in conceiving next time.[2] Studies show that miscarriage is one of the most common pregnancy complications and one out of every five pregnancies end in miscarriage out of which three-quarters occur in the first twelve weeks of pregnancy.[3] When pregnancy is abruptly ended a woman faces a traumatic event that augments a severe mental shock.[4] Some several factors

and causes are associated with the termination of pregnancies. Some of these are medical reasons such as endocrine misbalances, infections, exposure to chemicals, chromosome abnormalities, and uterine abnormalities.5 Other factors that are associated with the termination of pregnancy are socio-demographic factors such as illiteracy, low economic status, violence such as emotional or severe physical violence, poor social support, lack of antenatal care, and maternal age. Maternal age is a vital factor that contributes to the complications of pregnancy. Mothers aged less than 20 years and more than 35 years are more likely to have spontaneous abortions.[6] Several studies provide evidence that termination of pregnancies is common among women married as children. According to Child Marriage Facts and Figures, "One-third of girls in the developing world are married before the age of 18 and 1 in 9 are married before the age of 15.[7] In 2010, 67 million women 20-24 around the world had been married before the age of 18. If present trends continue, 142 million girls will be married before their 18th birthday over the next decade. That is an average of 14.2 million girls each year. While countries with the highest prevalence of child marriage are concentrated in Western and Sub-Saharan Africa, due to population size, the largest numbers of child brides reside in South Asia". Nasrullah, Muazzam, Bhutta & Raj, 2013 state that a high proportion of early marriages in Pakistan are a great apprehension that results in poor fertility outcomes including, pregnancy termination. Under-age marriages are an emerging public health issue in Pakistan.[8] Both boys and girls are victims of child marriages although girls are excessively affected. Child marriage is practiced extensively and can lead to a lifetime of disadvantage and deprivation. Studies show that women who are married at an early age are more likely to be uneducated, poor, live in rural areas, and have less access to health care services which contributes to maternal mortality and morbidity leaving an adverse effect on the health of women.[9] Strong association has been found between the maternal mortality, morbidity, and age of the mother. A great chance of adverse obstetric outcomes can occur in the case of teenage pregnancies (Khan & Jamal, 2003).[10] Given this backdrop child marriage is a phenomenon that should be studied in relation to other socio-demographic factors which are associated along with underage marriages that in turn result in complications in form of maternal mortality and morbidity. It is difficult to understand what factors are associated with the pregnancy complications in young pregnant females and to what extent. Hence there is an important need, use a well-designed study to examine the associated factors that lead to pregnancy complications in women married at an early age in Pakistan. This study aims to find the association of factors in teenage mothers that lead to termination of pregnancy.

MATERIAL AND METHODS

It is a cross-sectional study. The data was selected from Pakistan Demographic and Heath Survey (PDHS) 2012-2013 and secondary analysis was done. In Pakistan, PDHS is the fifth-largest national survey and 3rd consecutive worldwide research project, implemented by ORC (opinion research company), Macro, and financed by USAID. DHS has become the gold standard of survey data in developing countries. This survey is conducted after every 3-5 years. It contains a wide range of information on health issues and determinants of health. This survey is either conducted in Urdu language or any other regional languages such as Punjabi, Sindhi & Pashto. It consists of a sample of over 95,000 households in Pakistan. However, some areas, such as FATA, FANA, and AJK were not included in the survey due to security reasons. Numerous modules on malaria, fertility, child immunization, nutrition, and reproductive age female's health were considered in this survey. We defined early age marriage as <18 years of age. Analysis of secondary data was done in this study. This data is publicly available so ethical approval from any institution was not

required. To represent estimates of the national population all data was entered and analyzed using SPSS 21 version. Our analysis was limited to women married as children that are, 10-17 years of age.

The sample comprises of n= 5694 women with age at first cohabitation to assess the factors associated with pregnancy complications among early aged married women. 10,601 women who were married aged 15-49 years were recognized in DHS, of whom 10,023 were interviewed successfully (response rate 95%). A sample of ever-married females 10-17 years of age (n= 5694) was selected. All participants were assessed for demographic information by asking questions regarding their "age", "educational status", "region", "type of place of residence", "respondent's employment status", "partner's education status", "told about pregnancy complications", "violence (physical & emotional) during pregnancy", "number of antenatal visits", "blood relation with husband" and "socioeconomic status". Socio-economic status was calculated between 1 (poor), 2 (middle), and 3 (rich). Violence can be assessed by asking a question if the respondent experienced any emotional violence or husband/ partner ever hurt her during pregnancy. No. of antenatal visits categorized into less than 4 and 4-10 visits. World health organization (WHO) recommended four visits in normal cases. We assessed pregnancy complications in terms of two main outcomes (i.e. miscarriages/abortions and stillbirths) in this study. Pregnancy termination before seven months is called a miscarriage and after seven months it is called a stillbirth. These outcomes will be assessed by asking the question to respondents whether they ever had a terminated pregnancy. A total sample of females aged 10-17 years was analyzed for the prevalence of early age marriage and its statistics. Statistical significance was calculated for categorical variables. We considered a two-tailed p value less than 0.2 to be statistically significant. Using logistic regression models associations between early age marriages and pregnancy complications (miscarriages and stillbirths) were evaluated by calculating odds ratio (OR) with a 95% confidence interval after controlling for age and demographics. We assessed model fit using the "Hosmer-Lemeshow test goodness-of-fit test" (P-value < 0.05). Further multivariate analysis was done on the variables which were significant at <0.2 P value.

RESULTS

The sample consisted of 5694 women who married as children from age 10-17. Out of 5694 women, 1217 (21.4%) were married at the age of 10-14 and 4477 (78.6%) were married at the age of 15-17. They were selected from the areas of Punjab (22.9%), Sindh (22.9%), Baluchistan (16%), Khyber Pakhtunkhwa (21.8%), Gilgit Baltistan (12.4%), and Islamabad (4%). 2324 (40.8%) of which are living in urban areas and 3370 (59.2%) are residents of rural areas of Pakistan. The majority of these participants are uneducated (69.6%). More than half (78.5%) of the respondents were unemployed. 48.3% were having poor economic status while 31.8% were rich, the rest of them belong to the middle class. Partners of 39.2% women were uneducated while others had primary (15.4%), secondary (29.4%), and higher (16%) levels of education. Participants were asked if they were told about pregnancy complications, more than half (51.3%) were told about the complications while 48.7% were unaware of pregnancy complications. 2105 (37%) women had experienced pregnancy termination and 3589 (63%) did not experience termination. More than half of the respondents (65%) had cousin marriages. A higher number of respondents with child marriages were poor, uneducated, living in rural areas, and had not ever experienced any type of violence (emotion, physical or severe). 1445 (73.1%) i.e. more than half of the women had less than four antenatal visits. Respondents with ages 10-14 were more likely to have terminated pregnancies (22.3%) while women who were of the same age group and did not experience pregnancy

termination were less (20.8%). Respondents aged 15-17 years were less likely to have terminated pregnancy (79.1%) as compared to those who had terminated pregnancy (77.6%). The uneducated women were more likely to experience termination of pregnancy (72.6%) as compared to those who were educated (27.2%). The percentage of women who were unemployed and experiencing fewer terminations was slightly higher (80.7%) as compared to those who did not ever have terminated pregnancy (74.5%) among the same unemployed group while women who were employed were more likely to have terminated pregnancies (25.4%) as compared to those who did not experience pregnancy termination (19.2%).

Table-1: Prevalence of child marriage and socio demographic factors among ever married females aged 10-17 years, Pakistan Demographic and Health Survey 2012-2013. (n=5694)

Variables	Frequency	Percentage
Age of respondent at first cohabitation		
10-14	1217	21.4
15-17	4477	78.6
Region		
Punjab	1306	22.9
Sindh	1305	22.9
Khyber Pakhtunkhwa	1242	21.8
Baluchistan	909	16.0
Gilgit Baltistan	706	12.4
Islamabad (ICT)	226	4.0
Type of place of residence		
Urban	2324	40.8
Rural	3370	59.2
Highest Education level		
No education	3967	69.6
Primary	773	13.6
Secondary	758	13.3
Higher	196	3.4
Wealth Index		
Poor	2748	48.3
Middle	1136	20.0
Rich	1810	31.8
Told about pregnancy complications		
No	991	48.7
Yes	1042	51.3
Husband/partner's education level		
No education	2227	39.2
Primary	875	15.4
Secondary	1667	29.4
Higher	908	16.0
Respondent currently working		
No	4459	78.5
Yes	1223	21.5
Ever had a terminated pregnancy		
No	3589	63.0
Yes	2105	37.0
Experienced any injuries due to violence		
No	1393	89.3
Yes	167	10.7
Blood relation with husband		
No	1990	35.0
Yes	3701	65.0
Experienced any emotional violence		
No	1018	65.2
Yes	544	34.8
Experienced any less severe violence		
No	1066	68.2
Yes	496	31.8
Experienced any severe violence		
No	1435	91.9
Yes	127	8.1
Husband/Partner: who hurt respondent during pregnancy		
No	1337	88.7
Yes	171	11.3
No of antenatal visits		
<4	1445	73.1
4-10	531	26.9

The study did not find any significant association of early age marriage with pregnancy termination (OR 0.825, 95% CI 0.672-1.013, P value 0.179), the respondents resided in regions of Punjab (OR 0.901, 95% CI 0.675-1.201), Sindh (OR 0.893, 95% CI 0.670-1.191), Khyber Pakhtunkhawah (OR 0.863, 95% CI 0.646-1.152), Baluchistan (OR 0.772, 95% CI 0.573-1.041), Gilgit Baltistan (OR 0.755, 95% CI 0.555-1.027).

Table-2: Prevalence of termination of pregnancy among females aged 10-17 years by sociodemographic factors. Pakistan Demographic and Health Survey 2012- 2013.

Age of respondent at first cohabitation	Ever had terminated pregnancy		Odds ratio	95% CI	p-value
	No %	Yes %			
10-14	20.8	22.3	0.825	0.672 – 1.013	0.179
15-17	79.1	77.6	1		
Region					
Punjab	22.4	23.7	0.0901	0.675 – 1.201	0.195
Sindh	22.5	23.5	0.893	0.670 – 1.191	0.476
Khyber Pakhtunkhwa	21.7	21.9	0.863	0.646 – 1.152	0.441
Baluchistan	16.5	14.9	0.772	0.573 – 1.041	0.317
Gilgit Baltistan	12.9	11.4	0.755	0.555 – 1.027	0.090
Islamabad (ICT)	3.7	4.3	1		
Type of place of residence					
Urban	40.4	41.4	1		
Rural	59.5	58.5	0.958	0.859 – 1.068	0.439
Highest Education level					
No education	67.9	72.6	1.883	1.355 – 2.619	0.000
Primary	14	12.8	1.610	1.129 – 2.298	0.000
Secondary	13.9	12.1	1.530	1.071 – 2.185	0.009
Higher	4	2.3	1		0.019
Wealth Index					
Poor	48.8	47.3	0.889	0.796 – 1.017	0.168
Middle	20.2	19.3	0.887	0.760 – 1.034	0.090
Rich	30.8	33.3	1		0.125
Told about pregnancy complications					
No	51.1	44.5	0.766	0.639 – 0.918	0.004
Yes	48.8	55.4	1		
Husband/partner's education level					
No education	38.9	39.6	0.996	0.828 – 1.335	0.428
Primary	15	16	1.046	0.864 – 1.267	0.964
Secondary	30	28.1	0.918	0.776 – 1.085	0.642
Higher	15.8	16.1	1		0.315
Respondent currently working					
No	80.7	74.5	1		0.000
Yes	19.2	25.4	1.438	1.264 – 1.635	0.000
Experienced any injuries due to violence					
No	90.6	87	1		0.246
Yes	9.3	12.9	1.433	1.037-1.980	0.029
Blood relation with the husband					
No	36.1	32.8	1		
Yes	63.8	67.1	1.157	1.033 – 1.296	0.012
Experienced any emotional violence					
No	66.6	62.7	1		
Yes	33.3	37.2	1.189	0.960 – 1.472	0.112
Experienced any less severe violence					
No	70.9	63.7	1		
Yes	29	36.2	1.393	1.120 -1.731	0.003
Experienced any severe violence					
No	93.1	89.8	1		
Yes	6.8	10.1	1.529	1.062 – 2.202	0.022
Husband/Partner: who hurt respondent during a pregnancy					
No	89.1	87.9	1		
Yes	10.8	12	1.119	0.810 – 1.546	0.496
No of antenatal visits					
<4	74.5	70.6	0.825	0.672 – 1.013	0.066
4-10	25.4	29.3	1		

There was significant association found between all levels of education i.e. no education (P value 0.000), primary (P value 0.000), secondary (P value 0.009) and higher (P value 0.019), weather respondent was told about pregnancy complication (OR 0.766, 95% CI 0.639-0.918 P value 0.004), employment status (OR 1.438, 95% CI 1.264-1.635, P value 0.000) less severe violence (OR 1.393, 95% CI 1.120-1.731, P value 0.003), severe violence (OR 1.529, 95% CI 1.062-2.202, P value 0.022), blood relation with husband (OR 1.157, 95% CI 1.033-1.296, P value 0.012) and less than four antenatal visits (OR 0.825, 95% CI 0.672-1.013, P value 0.066) and termination of pregnancy.

Table-3: Factors associated with the termination of pregnancy among females aged 10-17 years by socio-demographic factors. Pakistan Demographic and Health Survey 2012-2013.

	AOR	95% CI	p-value
Highest Education Level			
No education	1.820	0.614-5.389	0.690
Primary	1.642	0.533-5.061	0.280
Secondary	1.933	0.617-6.060	0.388
Higher			0.258

DISCUSSION

This study has assessed that among 10-17 years females, 1217 (21.4%) had their first cohabitation in the range of age 10-14 while more than half (78.6%) of the women had their first cohabitation in the range of 15-17 years of age according to PDHS data. Most of these women had poor socio-economic status. They were an inhabitant of rural areas, poor and uneducated. However, taking into account these inequalities, females married as children had many other factors that were associated with pregnancy terminations. These findings indicated that early age marriages are a huge concern for Pakistan and are contributing to drastically increased risk of maternal morbidity and mortality of the whole country (Nasrullah, Zakar &Krämer, 2013).[11] Present study adds to the literature by showing that, women who get married at an early age experience more pregnancy complications. However, despite early age and social inequity indicators such as poor economic status, low education level, and rural residence some more factors are involved in the onset of pregnancy complications like miscarriages and stillbirths. These factors include employment status of women, cousin marriages, physical and emotional violence, number of antenatal visits taken, poor socio-economic class, and rural residency. Isaranurug, Mo-Suwan & Choprapawon, 2006; Taffa, 2003 stated that sociodemographic characteristics of individuals such as illiteracy, socioeconomic status, social support, and lack of antenatal care also affect pregnancy complications including termination of pregnancy.[12,13] In addition to the above-mentioned factors pregnant teenagers experience an increased risk of maternal complications like pre-eclampsia, eclampsia, hypertension, cephalon pelvic disproportion, delayed labor (Kumar, Singh, Basu, Panday & Bhargava, 2007; Goonewardene, Waduge, 2005).[14]
(United Nations Children's Fund [UNICEF]) (2005) reported that girls married at an early age are less likely to have awareness about issues of reproductive health. Obtaining healthcare may be difficult for them because of the barriers such as financial problems, powerlessness, and low education level.[15] They need to take permission from husbands or in-laws which can thus lead to an increase in the risks of morbidity and maternal mortality for teenage mothers. Pakistan ranks 100th regarding 'gender empowerment by the United Nations Development Program out of 102 countries, showing low female empowerment and a high level of gender inequality.[16] Girls married at an early age are

not empowered to make their own decisions, considering these social inequalities these females also experience some emotional and physical violence and therefore increased risk of maternal morbidity and mortality. Our study advances in the literature that pregnancy complications have a strong association with <4 antenatal visits that also attributed to a socially and economically dependent female. Contrary to findings in previous studies that showed a significant relationship between teenage mothers and termination of pregnancy, our study did not find a significant relationship between early age marriages and pregnancy complications. We found a significant association with social indicators and we can conclude that experiencing violence, having blood relation with husband, taking fewer antenatal visits, low education level and employment status affect pregnancy complications such as termination of pregnancy.

The limitations of this study are that data available from PDHS which is a secondary source of data so we were not able to involve other biological factors which might affect pregnancy complications in teenage mothers. Secondly, the outcome variable is not properly explained whether pregnancy termination is by force, violence, induced abortion, or natural termination. Moreover, the presence of a large number of missing values in more relevant variables i.e. BMI (body mass index) of mothers in PDHS data, which were considered in other studies. This study is done on women aged 10-17 years so its results cannot be generalized, to all women of reproductive age in the country. Furthermore, some qualitative and longitudinal studies are needed to explore more factors that may involve in provoking complications in teenage pregnancies.

Hence, the findings support the contribution of socio-cultural factors that provoke child marriages. Effective interventions are needed to prevent child marriages like engaging all levels of socio-political systems to raise awareness and manifestation of law regarding child marriages and adherent violence with special reference to pregnancy complications. Moreover, empowering females by increasing education; creating job opportunities, promoting civil, sexual, and reproductive health rights, and improving the role of women in family decision-making can help in reducing child marriages.

AUTHOR'S CONTRIBUTION

AT: Data analysis, Manuscript writing, and Reference management
RZ: Supervision of manuscript writing
BSK: Data analysis
MFH: Discussion
RA: Methodology

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Original Article

SELF-REPORTED SURVEY ON MEDICINAL USES OF CANNABIS IN HEALTH PROFESSIONALS

Sana Masood[1], Shaikh Hassan Bin Tariq[2], Asma Khanani[3], Hafsa Jawed[4], Wajiha Anzar[5], Ambrina Qureshi[6]

ABSTRACT

Background: Since the medicinal use of cannabis is well-known, there was a need to assess the knowledge, beliefs and experience regarding indications, safety and side effects of prescribing medicinal cannabis among Pakistani health workers.

Material and methods: A cross-sectional survey was conducted among medical and dental students and practitioners selected from different campuses of the two public sector medical universities of Karachi. A self-reported questionnaire was used to record knowledge, beliefs and experience regarding indications, safety and side effects of prescribing medicinal cannabis on a 5-point Likert scale. Data & analyzed was described using IBM SPSS Statistics for Windows, v. 24.0.

Results: A total number of 126 health professionals participated in this study with mean age 24.3 ± 2.5 years and more female (n=90) than males (n=36). The overall distribution of knowledge scores was obtained for 'neutral opinion'. Majority believed that medicinal cannabis can be used for treatment of dementia, chronic non-cancer pain, epilepsy and has anti-tumor effects.

Conclusion: It can be concluded that medicinal cannabis knowledge is limited among health care professionals. Measures must be taken to eliminate the knowledge gap of the health care providers about effectiveness and qualifying conditions of these products.

Key Words: Cannabis, Knowledge, Safety

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INTRODUCTION

Cannabis, also known as marijuana, is a psychoactive drug derived from Cannabis plant. This plant being a native to Central. Asia and Indian sub-continent is widely used as a recreational and entheogenic drug and in many traditional medicinal uses for centuries According to United Nation Office on Drug and Crime, it is the most widely produced and cultivated drug with approximately 182.5 million users globally.[1] Of the 483 known compounds derived, the main psychoactive component, tetrahydrocannabinol (THC), tends to provide feeling of ecstasy and euphoria to the consumer.

It can be used by smoking, vaporization, within food, or as an extract. The THC causes the "high" that people feel bringing changes to mood, altered states of mind and sense of time, difficulty with thinking and problem-solving, impaired memory with hallucinations and delusions depending upon the dose consumed.[2] The use of smoked high potency cannabis (HPC) with high

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concentration of THC and low concentration of cannabidiol (CBD) in psychotic patients is found to have poorer disease outcome as compared to ones who are non-cannabis smokers or who stopped cannabis use.[3,4] The continued use of HPC may lead to increased psychotic episodes and probability of re-hospitalization.[5] However, a survey reported that use low THC/CBD ration in smoked cannabis has been linked to fewer psychotic episodes as compared to ones with high THC/CBD ratio.[6] Furthermore, co-administration of CBD and THC induce less anxiety and fewer psychotic symptoms as compared to THC alone.[7,8]

The THC seems to be responsible for the psychogenic effect of cannabis, whereas CBD may inhibit THC induced psychosis. Therefore, prescribing cannabis with low THC and/or high CBD may reduce harm i.e., allowing cannabis use with less psychotic episodes and less chances of re-hospitalization. Many countries around the globe have now legalized the cultivation of cannabis for research purpose and medicinal use of cannabis. With the increasing evidence, the Federal Government of Pakistan on Tuesday, September 1, 2020 also approved the legalization of cannabis production.[9] Since its medicinal use is well-known, there was a need to assess the knowledge and attitude of medicinal use of cannabis among health workers. Therefore, this survey among Pakistani General Practitioners and Dentists was conducted with an aim to assess their knowledge, beliefs and experience regarding indications, safety and side effects of prescribing medicinal cannabis.

MATERIAL AND METHODS

A cross-sectional survey was conducted for the duration of three months (February 2021-April 2021). Health care professionals who gave consent were included in this study which comprised of medical and dental students as well as practitioners of different campuses of two public sector universities of Karachi.

A self-reported questionnaire was used as a data collection tool which was designed on Google forms. Questionnaire comprised of 4 sections; each section had various questions based on 5-point Likert scale with scores ranging from 0 (Strongly Disagree) to 4 (Strongly Agree). The first part consisted of questions to assess knowledge among health professionals on prescribing cannabis and its related benefits and side effects. The second part constituted a list of diseases and conditions and practitioners were asked whether they support the use of cannabis in such conditions. The third part focused on knowledge and belief on the major side effects of medicinal cannabis whereas the last part consists of questions to evaluate their belief on whether the hazardous effects of cannabis were more as compared to other drugs.

Data was analyzed using IBM SPSS Statistics for Windows, v. 24.0. Descriptive statistics like frequencies and percentages were obtained for categorical variables whereas mean and standard deviation was calculated for descriptive variables.

RESULTS

A total number of 126 health professionals participated in this study. General characteristics of participants showed that their mean age was 24.3 ± 2.5 years. Results revealed that there were greater number of female participants than males, (n=90, 71.4%) and (n=36, 28.5%) respectively. Sample comprised of participants from both medical and dental fields however, medical health professionals constituted the greatest frequency (n=65, 51.5%) where as those belonging to dental filed were slightly lesser in number (n=61, 48.4%). When the participants were inquired about their working experience more than half of respondents (n=77, 61.1%) reported < 2 years of experience in their working field whereas (n=49, 38.8%) had ≥ 2 years of experience. When the level of participants was assessed, it was seen that there was more participation by students (n=72, 57.1%) than practitioners (n=54, 42.2%) (Table 1).

Table 1: Description of survey participants (n=126)

Characteristics	Categories	No (%)	Mean ± SD
Age (yrs.)	---	---	24.3 ± 2.5
Experience (yrs.)	< 2	77 (61.1)	
	≥ 2	49 (38.8)	
Gender	Male	36 (28.5)	
	Female	90 (71.4)	
Profession	Medical	65 (51.5)	
	Dental	61 (48.4)	
Level	Student	72 (57.1)	
	Practitioner	54 (42.8)	

Perceived knowledge about cannabis

Perceived knowledge regarding cannabis in health professionals was assessed in form of various questions, through which scores for knowledge was calculated (Table 2). Surprisingly for most of the questions the participants had greatest frequency for 'neutral opinion', these questions included if their patients had ever been benefitted by the use of medical cannabis (n= 57, 45.2%), opinion regarding availability of cannabis for patients on prescription only (n= 45, 35.7%), level of comfort of health professionals in discussing use of medicinal cannabis with patients (n= 40, 31.7%), health professional's knowledge about the effect of various medicinal cannabis products (n= 41, 32.5%), ability of practitioner to prescribe medicinal cannabis (n= 41, 32.5%), current regulatory approaches towards its usage (n= 40, 31.7%), knowledge of health professionals in differentiating street cannabis and medicinal cannabis (n= 38, 30.1%), cannabis as the risk of abuse and dependence (n=40, 31.7%) , non-preference of cannabis prescription due to side effects (n=41, 32.5%) and opinion about the availability of sufficient scientific evidence regarding cannabis products consumption (n=64, 50.7%).

There were few questions over which the participants had 'strongly agreed', this included opinion about the preference of cannabis use by specialists with shared care (n=62, 49.2%), (n=44, 34.9%) respectively. Less frequency for the responses were obtained over which participants had 'strongly disagreed', this included awareness about different medicinal cannabis products (n=47, 57.1%) and practitioner's ability to help patients to access medicinal cannabis legally (n=49, 38.3%).

Table 2: Survey scores for perceived knowledge about cannabis in health professionals

Knowledge Variables	0	1	2	3	4
I have patients who may benefits from Medical Cannabis	44	11	57	9	5
Medicinal Cannabis products should be available on prescription now for certain indications	16	15	45	42	8
I feel comfortable discussing medicinal cannabis with my patients	12	34	40	32	8
I have good knowledge around the effects of medicinal cannabis products	39	25	41	16	5
I am aware of the different Medicinal Cannabis products and formulations currently available	47	31	30	13	5
I would like the ability to prescribe Medicinal Cannabis products	18	26	41	27	14
Medicinal cannabis should only be prescribed by specialists	13	12	13	26	62
Medicinal cannabis should be provided in "shared care" with a specialist	14	9	29	29	44
Only GPs who have undergone specific training and credentialing should be allowed to prescribe medicinal cannabis	15	19	14	28	50
I know how to help patients legally access medicinal cannabis	49	27	24	18	7
I understand the current regulatory approach to medicinal cannabis	37	26	40	16	7
There is little difference between "street cannabis" and medicinal cannabis products	19	27	38	24	18
I will not prescribe medicinal cannabis as the risk of abuse and dependence is too high	10	22	40	26	28
I will not prescribe medicinal cannabis as the risk of side effects (other than and dependence) is too high	18	23	41	28	16
There is sufficient scientific evidence of the efficacy of medicinal cannabis	8	21	64	23	10
Overall perceived knowledge score prevalence	**359**	**328**	**557**	**357**	**287**

0=strongly disagree, 1=disagree, 2=neutral, 3=agree, 4=strongly agree

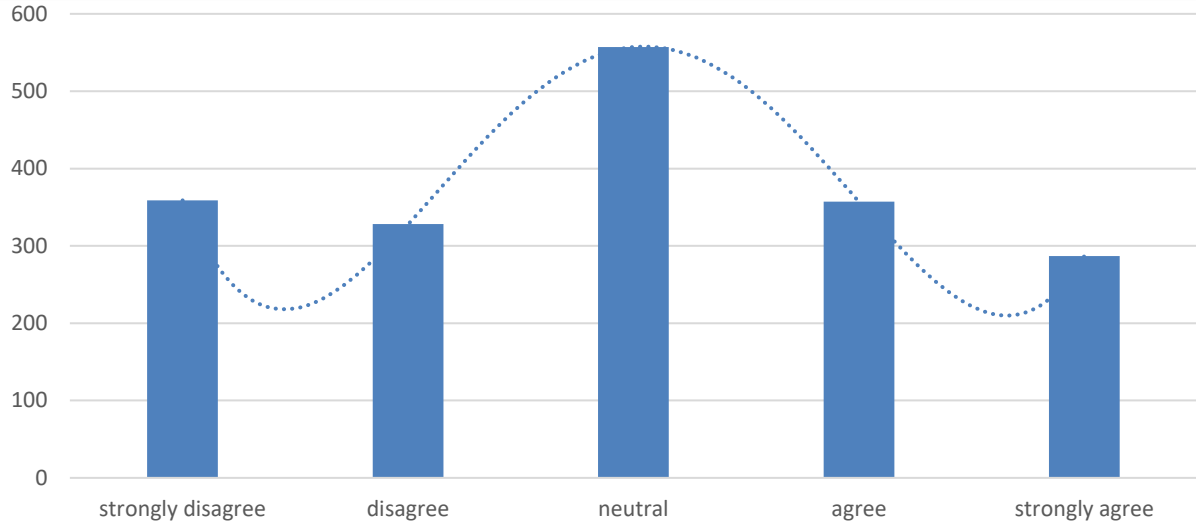

Figure 1: Overall distribution of perceived knowledge scores

Overall score for perceived knowledge for responses like 'strongly disagreed' was 359, for 'disagree' it was 328, 557 responses were recorded as 'neutral' whereas a score of 357 and 287 was recorded for 'agreed' and 'strongly agreed' respectively. Figure 1 shows overall distribution of perceived knowledge scores it clearly depicts that the greatest score was obtained for 'neutral opinion'.

Self-reported indications and side-effects

When the participants were inquired about self-reported indications and their perception about the possible usage, side-effects and contraindications of cannabis products, greatest frequency was obtained for 'neutral reviews'. Majority believed that medicinal cannabis can be used for treatment of various conditions. Amongst all greatest number of respondents believed that it can be used in treating dementia (n=50, 39.9%), followed by management of chronic non-cancer pain (n=47, 37.3%), epilepsy (n=46, 36.5%), some believed that it has anti-tumor effects (n=44, 34.9%), some respondents also believed that it has role in treating multiple sclerosis (n=42, 33.3%), providing palliative care (n=41, 32.5%), PTSD (n=37, 29.3), dealing with insomnia (n=34, 26.9%) and management of anxiety (n=33, 26.1%). Some 'strongly believed' that it also plays a role in treatment of chronic cancer pain (n=46, 35.7%), chemotherapy-induced nausea and vomiting (n=42, 33.3%), curing of neuropathic pain (n=41, 32.5%), managing severe depression (n=30, 23.8%) and managing cachexia in patients associated with severe illness (n=35, 27.7%)

When the questions were asked in order to assess perceived side effects of cannabis usage, majority had an opinion that its constant use as medicinal agent can be hazardous and can cause some serious conditions like weight gain (n=63, 50%), drug interactions (n=72, 39.6%), followed by psychosis (n=46, 36.5%), few impairments like driving impairment (n=38, 30.1%) and cognitive impairment (n=34, 26.9%), mental health issues (n=42, 33.3%) and delay in brain development (n=44, 34.9%).

When the participants were inquired about possible hazards of cannabis it was seen that the participants had neutral opinion, about the question that whether they think that medicinal cannabis are hazardous than prescription of opioids, benzodiazepines, antipsychotics, statins, chemotherapy drugs, antidepressants (Table3). Findings of this study show that most of the participants had some type of cannabis education, and the scores revealed that are participants are moderately aware and knowledgeable about these products.

Table 3: Self-reported indications, side-effects and hazards of medicinal use of Cannabis

Medicinal Cannabis may be used in?	**0**	**1**	**2**	**3**	**4**
Chronic Cancer Pain	23	4	23	45	31
Chronic non-cancer Pain	15	23	47	29	12
Neuropathic pain	20	15	37	41	13
Intractable epilepsy	20	15	46	32	13
Anti-tumour effects	16	19	44	32	15
Spasticity in Multiple Sclerosis	21	18	42	34	11
Dementia patients with agitation	19	16	50	28	13
Insomnia	25	32	34	23	12
PTSD	29	22	37	30	8
Anxiety	28	22	33	22	21
Depression	23	29	29	30	15
End of life / Palliative Care	14	18	41	33	20
Chemotherapy-induced nausea and vomiting	17	15	39	42	13
Cachexia associated with severe illness	15	23	33	35	20
Major Side effects could be?					
Addiction and dependence	16	14	22	24	50
Cognitive impairment	10	10	34	31	33
Driving impairment	7	11	38	35	27
Weight gain	6	10	63	25	14
Psychosis	7	12	46	28	25
Other long-term mental health issues	10	11	42	35	20
Interaction with other medications	6	9	50	35	18
Impact on the developing brain	8	7	44	35	24
Medicinal Cannabis are more hazardous than?					
Prescription opioids	17	12	41	33	15
Benzodiazepines	11	19	48	31	17
Antipsychotics	20	15	48	25	18
Statins	24	20	47	21	14
Chemotherapy drugs	25	19	45	24	13
Antidepressants	19	21	46	23	17

0=strongly disagree, 1=disagree, 2=neutral, 3=agree, 4=strongly agree

DISCUSSION

Throughout the world health care providers play a crucial role in facilitating patients to access medical cannabis.[10-12] Some of the previously reported literature suggested that only a minor population of health care providers believed that medicinal cannabis confers benefits to patients.[13,14] In present study, we assessed knowledge, awareness and perception about indications, contraindications and hazards of prescribing medicinal cannabis among health care providers. Findings of current study revealed that health professionals generally had 'moderate levels' of factual knowledge about these products. The average level of knowledge was moderate as majority had neutral opinion to variety questions (11 out of 15). Possible reason for this finding may be attributed to the fact that the scores were calculated on the basis of self-perceived knowledge. However, these results are in agreement with the study conducted by Philpot et al on-healthcare workers of Minnesota.[15] When the awareness was assessed regarding indications, contraindication and hazards of cannabis usage it was seen that majority had concerns related to it. Similar findings are congruent with a previous study by Kruger et al which revealed that healthcare providers were concerned with drug abuse, interactions, side-effects.[16]

It can be identified that the scores for knowledge obtained in present study is not enough to integrate cannabis into patient care. In the light of these findings, it is recommended that consistent clinical guidelines are required in order to reduce barrier between integration of medicinal

cannabis into health care system. Additionally, detailed information which is similar to FDA-approved medication is currently lacking from medicinal cannabis products which might be acting as a barrier.[17,18] Limitation of present study was that it was conducted in two public sector universities only which might be reason for 'moderate levels' of score, another possible explanation for this outcome might be the fact that both students and practitioners were included resulting in lower knowledge scores. Hence, large scale studies are recommended on similar topic.

CONCLUSION

It may be concluded that medicinal cannabis knowledge is limited among health care professionals. Measures must be taken to eliminate the knowledge gap of the health care providers about effectiveness and qualifying conditions of these products. Furthermore, clinical trials are also needed about how medical cannabis improves quality of life which will help in clinical decision making.

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Conflict of interest
The authors declare that there is no conflict of interest

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AUTHORS' CONTRIBUTION

SM: Wrote the manuscript.
SHBT: Collected and entered the data in software.
AK: Collected and entered the data in software.
HJ: Collected and entered the data in software.
WA: Interpreted the results and critically reviewed the manuscript.
AQ: Conceived the study idea, performed the analysis and supervised the study.

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Original Article

COMPARATIVE STUDY OF ENDOSCOPIC VS EXTERNAL DACRYOCYSTORHINOSTOMY

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ABSTRACT

Background: This study was carried out to compare the success rate of external and endoscopic dacryocystorhinostomy (DCR) in patients with nasolacrimal duct obstruction.

Material & Methods: Interventional study design was opted. Total 80 patients were divided into two groups with 40 patients in each group. Group 1 underwent external DCR while group 2 underwent endoscopic DCR in Akhtar Saeed Trust hospital from 1/2/2017 to 31/1/2020. The success rate of endoscopic group was compared with the external group in regular follow up after 7th post-op day, one month, 3 months, 6 months and one year. All the data was entered and analyzed with SPSS version 20. Quantitative variable like age was presented as mean and standard deviation. Qualitative variables were calculated in frequencies and percentages.

Result: The success rate in terms of relief of epiphora was 92.5% in endoscopic group as compared to 85% in external group.

Conclusion: The endoscopic DCR showed better results than the external DCR.

Key Words: Nasolacrimal duct, Epiphora, Dacryocystorhinostomy

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INTRODUCTION

Lacrimal drainage pathway starts from the lacrimal puncta and ends in the inferior meatus in the lateral wall of nose. It constitutes lacrimal puncta, lacrimal canaliculi, lacrimal sac, and nasolacrimal duct which ends in an opening in the inferior meatus. Obstruction at any level in the above pathway can cause epiphora (watery eyes). The primary acquired nasolacrimal duct obstruction is due to chronic inflammation resulting in fibrosis, stenosis, and closure of the duct ostium.[1,2]

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Nasolacrimal duct obstruction is the most common cause which can be relieved by a surgical operation dacryocystorhinostomy (DCR) which involves creation of a fistula that bypasses the obstruction and restores the tear flow.[3] The operative approach can be external or endoscopic. External DCR was the gold standard method even after the endoscopic approach had been described, because of limited technology at that time with a success rate ranging between 80% to 100%.[4] However, the improvements in endoscopic visualization & instrumentation have made the endoscopic DCR a better choice these days.[5] In addition, endoscopic DCR has many benefits over external DCR i.eno external scar mark, quicker recovery and lower postoperative morbidity.[6] Various studies describe different success rates of endoscopic endonasal DCR from 89%to 98%.[7,8] This study was conducted to compare

the success rate of external and endoscopic dacryocystorhinostomy (DCR) in patients with nasolacrimal duct obstruction.

OPERATIONALDEFINITIONS

Success being defined as complete relief of epiphora plus patency on syringing at1 year follow up.
Ephiphora is overflow of tears onto the face.

MATERIAL AND METHODS

An interventional study was conducted to do a comparative analysis of endoscopic DCR with external DCR. Eighty lacrimal systems of 80 patients coming to Akhtar Saeed Trust Hospital from 1/2/2017 to 31/1/2020 (three years) were selected. Non-probability type of purposive sampling technique was used for data collection. The patients were selected after detailed ENT examination and opinion from the ophthalmology department. Patients fulfilling the inclusion criteria with isolated lacrimal duct obstruction on syringing, were included in the study. While patients having canalicular obstruction assessed by syringing, were excluded from the study.

The patients were randomly divided into two groups 1 and group 2. Informed consent was taken from the patients. Group 1 underwent external DCR while group 2 underwent endoscopic DCR. Silicon lacrimal tube was removed 12 weeks after surgery. Outcome was compared at 7th postoperative day, 1st month, 3rd month, 6th month and 1 year. S. A standard Performa was used for data collection and the following variables were recorded including age, gender, relief of epiphora on 7th post operative day, 1 month, 3 month, 6 month and one year consecutively. Success rate of either of the procedures in terms of relief of epiphora and patency of syringing at interval of one year was labeled and charted in the table. Demographic profile and relevant data was recorded on research tools. Data was entered and analyzed with SPSS version 22. Quantitative variable like age was presented by calculating mean and standard deviation. Qualitative variables were presented by calculating frequencies and percentages. Out of total 80 participants, 33(41.25%) were males and 47(68.75%) were females.

RESULTS

Out of total 80 participants, 33(41.25%) were males and 47(68.75%) were females.

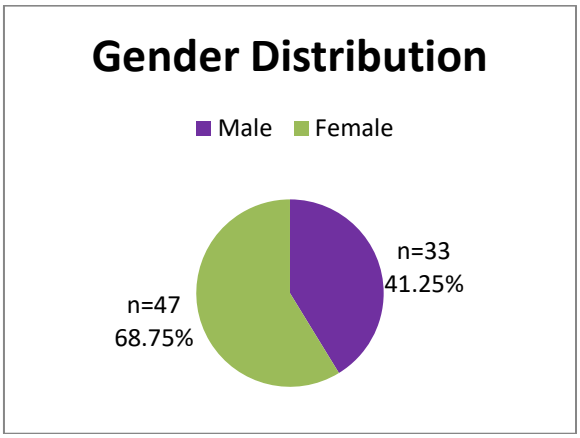

Figure-1: Gender Distribution of Respondents

Table-1: Age Distribution of Respondents

Total number	Mean Age in years	Standard deviation	Minimum	Maximum
80	41.3	13.192	12	64

The mean age of the participants was 41.3±13.19 years.

Table 2 revealed that the relief of epiphora on 7th day was high (95%) in endoscopic group as compared to external group (90%). After the period of one month, relief of epiphora in endoscopic group was 95% while in external group, the percentage dropped and only 87.5% reported the relief of epiphora. A drop in percentage was also observed in endoscopic group after 3 months to 92.5% whereas in endoscopic group, it remained at 87.5%. After 6 months interval, relief of epiphora in endoscopic group was 92.5% while in external group, the percentage dropped to 85% for relief of epiphora. After a period of one year, relief of epiphora reported in endoscopic group was 92.5% as compared to external group, in which percentage for the relief of epiphora further dropped to 82.5%.

Table-2: Comparison of Outcome of DCR Procedures

Outcome of Procedure			Type of DCR Procedure			p-value
			External	Endoscopic	Total	
Relief of epiphora on7th day	Relief	Frequency	36	38	74	0.03
		Percentage	90%	95%	92.5%	
	No relief	Frequency	4	2	6	
		Percentage	10%	5%	7.5%	
Total			40	40	80	
Relief of epiphora at 1month			External	Endoscopic	Total	p-value
	Relief	Frequency	35	38	73	0.02
		Percentage	87.5%	95%	91.25%	
	No relief	Frequency	5	2	7	
		Percentage	12.5%	5%	8.75%	
Total			40	40	80	
Relief of epiphora at 3 months		Count	External	Endoscopic	Total	p-value
	Relief		35	37	72	0.02
		Percentage	87.5%	92.5%	90%	
	No relief	Count	5	3	8	
		Percentage	12.5%	7.5%	10%	
Total			40	40	80	
Relief of epiphora at 6months			External	Endoscopic	Total	p-value
	Relief	Frequency	34	37	71	0.03
		Percentage	85%	92.5%	88.75%	
	No relief	Frequency	6	3	9	
		Percentage	15%	7.5%	11.25%	
Total			40	40	80	
Relief of epiphora at 1 year			External	Endoscopic	Total	p-value
	Relief	Frequency	33	37	70	0.02
		Percentage	82.5	92.5%	87.5%	
	No relief	Frequency	7	3	10	
		Percentage	8.75	7.5%	12.5%	
Total			40	40	80	

Table 3 showed that the patency was 100% in endoscopic group DCR at one year after procedure, while in external group DCR, patency was 92.5% which revealed that the endoscopic procedure was more effective.

Table-3: Patency on Syringing at 1 Year

Procedure	Outcome	Type of procedure		Total
		External DCR	Endoscopic DCR	
Patency on syringing at 1year	Patent	37(92.5%)	40(100%)	77(96.25%)
	Not patent	3(7.5%)	0(0%)	3(3.75%)
Total		40	40	80

DISCUSSION

In this study, out of the 80 patients, 47 (68.75%) were females and 33 (41.25%) were males. we compared two groups of lacrimal sac surgery. Group 1 underwent external dacryocystorhinostomy and group 2 had endoscopic dacryocystorhinostomy. On 7th postoperative day, 36 (90%) lacrimal systems in group 1 showed relief of epiphora whereas 38 (95%) lacrimal systems in group 2 showed relief of epiphora. On 1 month follow up, the values for relief of epiphora in group 1 were 35(87.5%) and 38(95%) in group 2. On 3rd month follow up, the values for relief of epiphora in group 1 remained same as 35(87.5%) whereas in group 2 the values were reduced but still much higher than group 1 at 37(92.5%). The values for relief of epiphora at 6 months were reduced to 34 (85%) in group 1 and were stable at 37(92.5%) in group 2. On 1 year follow up, the values were further reduced to 33(82.5%) in group 1, while in group 2, values remained stable at 37(92.5%). One year follow up patency of the lacrimal systems in both groups were assessed by syringing and 40(100%) lacrimal systems in group 2 were found to be patent, while in group I, 37(92.5%) lacrimal systems were found to be patent. This difference is statistically

significant (p-value = 0.007) and is comparable to the figures that are given in the international studies.[9-12]

CONCLUSION

Endoscopic dacryocystorhinostomy (DCR) not only provides significantly better results than External DCR in terms of relief of epiphora, but it is also cosmetically more acceptable to the patient with no external scar mark on the face after surgery. We suggest using this technique more commonly for the patients of nasolacrimal duct obstruction.

AUTHOR'S CONTRIBUTION

ZIB: Concept of study and Review
AHS: Data analysis and review critically
MDS: Literature review
SR: Data collection

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Original Article

PROPHYLACTIC LOW DOSE KETAMINE IN PREVENTING PERI-OPERATIVE SHIVERING DURING SPINAL ANESTHESIA IN ORTHOPEDIC PATIENTS: A PROSPECTIVE RANDOMIZED DOUBLE-BLIND STUDY

Fareha Iram Khosa[1], Taoseef Ahmed[2], Usman Tahir[3], Syed Kashif Raza Rizvi[4], Adnan Sadiq[5], Shazia Abid[6]

ABSTRACT

Background: After spinal anesthesia, shivering is reported to occur in 36 - 85 % of the cases. Physical techniques like external heating or pharmaceutical interventions are often used to avoid peri-operative hypothermia and shivering. This study aimed to assess the effectiveness of low dose ketamine in preventing peri-operative shivering during spinal anesthesia in orthopedic patients

Material and Methods: This was a prospective randomized double-blinded study done at the Department of Anesthesia and Pain Management, The Indus Hospital, and Health Network Raiwind Campus Lahore for four months. 60 patients were incorporated. Group 1 patients (n=30) were given a low dose of ketamine (0.2 mg/kg iv) after spinal anesthesia while group 2 patients (n=30) were given 5ml of saline after spinal anesthesia. Axillary/frontal temperature was measured at 0, 15, and 30 minutes after spinal anesthesia.

Results: In group 1, shivering was observed in 1 (3.33%), 1 (3.33%) and 3 (10%) patients after 0, 15 and 30 minutes respectively while in group 2, shivering was observed in 0 (00), 6 (20%) and 11 (36.67%) patients after 0, 15 and 30 minutes respectively (p=0.006). In group 1, rescue maneuver was used in 4 (13.33%) patients while group 2 rescue maneuver was used in 14 (46.67%) patients. This difference was statistically significant (p=0.005)

Conclusion: Our study concludes that prophylactic Low dose ketamine is effective in preventing peri-operative shivering during spinal anesthesia in orthopedic patients as compared to the placebo group.

Key Words: Ketamine, Shivering, Spinal anesthesia

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INTRODUCTION

In humans, thermal stimuli are processed at the anterior hypothalamus level. The typical core temperature of the human body is 36.5°C–37.5°C, with a 0.2–0.4°C inter-threshold range. If the temperature drops below this threshold, responses to warm the body are triggered.[1] Vaso-dilation caused by regional anesthesia enables heat transfer from the core to the periphery, resulting in vasoconstriction and shivering above the block level.[2] Shivering is described as a

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perceptible fasciculation or tremor lasting more than 15 seconds in the Jaw, face, trunk, head, or extremities.[3] After spinal anesthesia, shivering is reported to occur in 36 – 85 % of cases.[4,5] The thermoregulation system is affected by spinal anesthesia because it inhibits tonic vasoconstriction, which is important for the regulation of temperature.[6] Although the specific cause of shivering during spinal anesthesia is unknown, hypotheses have been proposed to explain it.[7-9] The heat is transferred internally from the core to the peripheral region. Increased heat loss from body surfaces exceeds metabolic heat generation due to the lack of temperature regulation vasoconstriction below the blockage. There is a 0.5° C reduction in vasoconstriction and a small rise in the sweating threshold, indicating altered temperature regulation.[10]
Shivering during regional anesthesia is impacted by a variety of different parameters, including the number of spinal segments blocked, old age, a high degree of the spinal blockade, and the usage of ingredients in spinal anesthesia, all of which may have an impact on the regulatory systems. One of the most common unpleasant adverse effects of surgery is perioperative hypothermia and shivering. Because of its ability to impede norepinephrine absorption into postganglionic sympathetic nerve terminals, ketamine plays a function in thermoregulation.[11,12] By inhibiting norepinephrine absorption into postganglionic sympathetic nerve terminals and directly stimulating central sympathetic nerves, redistribution of heat might be reduced by ketamine to the periphery from the core.[13] After regional anesthesia, ketamine was beneficial in the prevention and treatment of shivering, although patients had hallucinations.[11,14] This study was piloted to determine the role of prophylactic low dose ketamine i.e 0.25mg/kg in preventing peri-operative shivering with fewer hallucinations during spinal anesthesia in orthopedic patients.

MATERIAL AND METHODS

This was a prospective randomized double-blinded study done at the Department of Anesthesia and Pain Management, The Indus Hospital, and Health Network Raiwind Campus Lahore for four months (**March-June**). Study approval was taken from the hospital's ethical and research committee. The inclusion criteria for our study were ASA 1 patients of both genders having age ranged from 18 to 60 years enrolled for orthopedic surgery under spinal anesthesia while the exclusion criteria were patients having >30 kg/m2 BMI with uncontrolled hypertension, patients having coronary problems, patients having high intracranial and intraocular pressure, patients not willing for spinal anesthesia and patients having known psychiatric problems. The sample size was calculated according to a previous study by considering intraoperative shivering as the main outcome.[20] In this previous study, the intra-operative incidence of shivering was 42.5% in the saline group while it was 2.5% in the Ketamine group.
In the above study, the incidence of intraoperative shivering in the saline group was 42.5% and incidence in the ketamine group was 2.5%. By taking the difference of 40%, power of 80%, and 95% confidence interval, the sample size needed was 21 in each group. Therefore, a total of 30 patients were incorporated in each group to allow for withdrawal or dropout. They were categorized into groups 1 and 2. Randomization was done by the lottery method. Consent form in written was taken from all the patients. 30 patients were included in each group. Group 1 patients were given intravenous pre-filled syringe group 1 drug i.e 5ml low dose of ketamine (0.25mg/kg diluted to form 5ml) after spinal anesthesia while group 2 patients were given pre-filled syringe group 2 drug i.e 5ml of saline after spinal anesthesia. A standard dose of 2ml of 0.75% bupivacaine at L3/4 or L5/4 interspace was injected. Axillary/frontal temperature was measured at 0,15 and 30 minutes after spinal

anesthesia. The operating room temperature was maintained at 24-26 C°. by adjusting air conditioners. The presence of mild to moderate shivering was observed at 0,15 and 30min according to. The Bedside Shivering Assessment Scale (Table 1) and recorded. Rescue drug tramadol 20 mg was given in case of mild to moderate shivering. Data were analyzed statistically by using SPSS version 23. For qualitative data mean (SD) was calculated while for quantitative data, frequency (percentages) were calculated. For comparison of shivering between the two groups, the Chi-square test was used.

Table 1: The Bedside Shivering Assessment Scale

Score	Definition
0	None; no shivering noted on palpation of the masseter, neck or chest wall
1	Mild: Shivering localized to the neck and/or thorax only
2	Moderate: shivering involves gross movement of the upper extremities (in addition to neck and thorax)
3	Severe: shivering involves gross movements of the trunk and upper and lower extremities

RESULTS

In this study, a total of 60 patients were included. There were 24 (80%) males and 6 (20%) females in group 1 while in group 2, there were 21 (70%) males and 9 (30%) females. (Figure 1) The mean (SD) age in group 1 was 37.24 (12.79) years while in group 2, the mean age was 37.43 (12.54) years. (Table 2) In group 1, shivering was observed in 1 (3.33%), 1 (3.33%) and 3 (10%) patients after 0, 15 and 30 minutes respectively while in group 2, shivering was observed in 0 (00), 6 (20%) and 11 (36.67%) patients after 0, 15 and 30 minutes respectively (p=0.006). (Table 3) In group 1, rescue maneuver was used in 4 (13.33%) patients while group 2 rescue maneuver was used in 14 (46.67%) patients. This difference was statistically significant (p=0.005) (Figure 2)

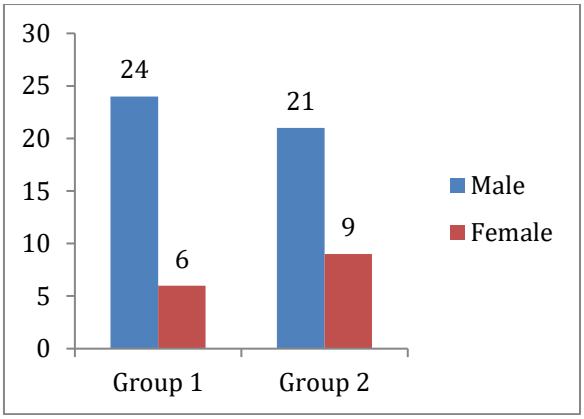

Figure 1: Gender wise distribution of patients in both the groups

Table 2: Age-wise distribution of patients in both the groups

Parameter	Group 1 (Years)	Group 2 (Years)
Mean age	37.24	37.43
Standard deviation	12.79	12.54

Table 3: Comparison of shivering in both the groups

Shivering	Group 1 N (%)	Group 2 N (%)
Shivering at 0 minutes	1 (3.33%)	0 (00)
Shivering at 15 minutes	1 (3.33%)	6 (20%)
Shivering at 30minutes	3 (10%)	11 (36.67%)

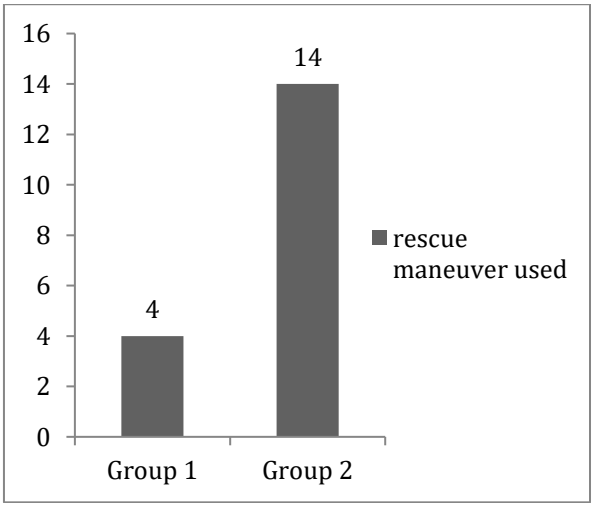

Figure 2: Rescue maneuver used in both the groups

DISCUSSION

A rise in metabolic activity, increased oxygen use (by 300–400%), and increased carbon dioxide generation are all associated with shivering. It induces arterial hypoxemia and lactic acidosis, as well as increased intraocular and intracranial pressures, as well as elevated cardiac activity, and peripheral vascular resistance.[15,16] Physical techniques like external heating[15] or pharmaceutical interventions are often used to avoid peri-operative hypothermia and shivering.[17-19] According to the literature, ketamine has been used in various studies for the treatment of shivering in various doses.[20, 21] In our study, in group 1, shivering was observed in 1 (3.33%), 1 (3.33%), and 3 (10%) patients after 0, 15 and 30 minutes respectively while in group 2, shivering was observed in 0 (00), 6 (20%) and 11 (36.67%) patients after 0, 15 and 30 minutes respectively (p=0.006).

In accordance with our study, a previous study by Kose et al. reported that there were few cases of shivering in patients treated with ketamine as compared to the placebo group.[22] While its function in thermoregulation has been linked to its anti-shivering effects, the precise mechanism by which ketamine works to counteract this effect is yet unknown. Another study was done by Shakya et al. also reported that shivering can be reduced effectively with ketamine after spinal anesthesia than saline.[20] Ketamine's vasoconstrictive characteristics reduce heat redistribution from the core to the periphery, limiting the drop in temperature that comes with spinal anesthesia. In addition to its effects on the periipheri, Ketamine has also been observed to have a central effect on thermoregulation at several levels, such as the hypothalamus and the locus coeruleus.[1,23] In group 1, rescue maneuver was used in 4 (13.33%) patients while group 2 rescue maneuver was used in 14 (46.67%) patients (p=0.005). In our study, a significant reduction in shivering was observed, in group 1patients as compared to group 2, by following them for two hours. This shows that ketamine has also anti-shivering ability post-operatively. Due to the huge volume of distribution and accumulation of ketamine after prolonged infusions, side effects such as abnormal liver function tests or psychomimetic problems might be developed.[24]

One of the recognized adverse effects of ketamine is hallucination, which has only been recorded in high dosages.[25] A previous study reported that a low dosage of ketamine effective in treating post-anesthetic shivering.[25] With the dosage utilized in our research, none of the patients had any side effects. The major limitation of our study was that shivering was not graded. The second limitation of our study is the small sample size.

CONCLUSION

Our study concludes that prophylactic Low dose ketamine is effective in preventing peri-operative shivering during spinal anesthesia in orthopedic patients as compared to the placebo group. No significant side effects were observed in our study. The ability of ketamine to minimize postoperative shivering should be studied in future trials and the ideal dose should be determined.

Abbreviations:

SPSS **(**statistical package for the social sciences)
SD (Standard deviation)
BSAS (Bedside shivering assessment scale).

AUTHOR'S CONTRIBUTION

FIK: Conception, design of work acquisition & analysis of data
TA: Writing research findings
UT: Outline of article & literature review
SKRR: Performa making
AS: Outline of article & literature review
SA: Data collection

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Original Article

HEALTH AND DISEASE STATUS OF FEMALE INMATES IN CENTRAL JAIL KARACHI: A CROSS-SECTIONAL STUDY

Naveed Mansoori[1], Syed Muhammad Mubeen[2], Noor-us-Sabah[3], Syed Ishtiaq Ahmed Fatmi[4]

ABSTRACT

Background: Globally, female prisoners represent about 7% of the total prison population. Women in prisons need special treatment due to their separation from their communities, homes, and families. There is a high incidence of chronic diseases among prisoners in many parts of the world.

Objective: The study aimed to identify the general health condition among female inmates in Karachi prison.

Material and Methods: A cross-sectional study was conducted during 2019. Data were collected from 100 women prisoners in Central Jail, Karachi using a non-probability convenient sampling technique. A pre-designed and pre-tested questionnaire was used to collect the data about health issues among women prisoners. Descriptive analysis was done and a Chi-square test was used to observe the association of different variables with disease status and time in imprisonment. p-value <0.05 was considered statistically significant.

Results: Out of 100 inmates, 30% suffered from different health problems and 49% were prisoned for more than 6 months. The majority of the prisoners (58%) were addicted, 96% used tap water for drinking and 73% were satisfied with sanitary conditions in prison. Statistically significant ($p<0.05$) difference was found between hypertension and allergic diseases with time spent in prison.

Conclusion: Female prisoners face many health problems during their imprisonment. Although sanitary conditions are satisfactory and treatment facility is available in prison, a significant proportion of female prisoners suffer from different acute and chronic diseases.

Key Words: Prison, Health, Women

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INTRODUCTION

The terms Jail and Prison are often used interchangeably but Jail is usually defined as the place in police stations where people who have been arrested or charged with a crime are held until they are either released or sentenced to prison and Prison is defined as a place where people who have been convicted of crimes are sent to serve their sentences. The jails and prisons are usually operated under the direct control of the district and provincial government, respectively.[1]

Worldwide, females constitute about 7% of total prisoners.[2] Prisoners are among the most susceptible population for acquiring a wide range of acute and chronic diseases. Communicable diseases are especially common in this population as the prisoners from different communities, carrying different risk factors are kept together for a varying times.[3] Moreover, they are also exposed to adverse living conditions

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prevailing in the jail, which includes poor management, inadequate food provision, congested and over-populated accommodation, poor ventilation, and sanitary conditions.[4]

Health care issues among women prisoners are rising day by day, which are not usually addressed satisfactorily by the authorities. The most frequently seen health problems among female inmates are poor hygiene, mental issues, communicable diseases, smoking, and substance abuse.[5-7]

In the United States, studies have demonstrated higher levels of hypertension, diabetes, asthma, obesity, and other major health issues among such female inmates.[8] In Australia, at least one chronic health issue was found out in 81% of female prisoners.[9] Nevertheless, the study conducted in Japan showed a reduction in blood pressure and dyslipidemia in female prisoners. It could be likely due to the enforced lifestyle changes in jails of Japan.[10]

A recent study conducted in Pakistan reported that 3.8% of female prisoners were Hepatitis C positive, 12.8% had hypertension, 18.8% had depression, 3.8% had active tuberculosis, and 83% of female prisoners were not satisfied with the available healthcare services in jail.[11]

Women's health has a significant impact on the community as a whole. After a thorough search for the relevant literature, it was identified that published data on this issue is scarce in Pakistan. The objective of this study is to identify the general health condition among female inmates in Karachi prison.

MATERIAL AND METHODS

A cross-sectional study was conducted at Central Jail, Karachi during 2019. A total of 100 women prisoners who gave informed consent were included using the non-probability convenient sampling technique. The approval was obtained from the Ethical Research Committee of Hamdard College of Medicine and Dentistry, Karachi, Pakistan.

The study tool used in our study was a pre-designed and pre-tested questionnaire. It was in Urdu. The questions were open-ended. Medical terms were avoided as far as possible or were explained by the researcher and were filled up with their support. The self-esteem and respect of the respondents were assured. Before the administration of the questionnaire, a briefing was given to the authorities and prisoners on the intent and different aspects of the study. It was also emphasized that collected data will only be used for research purposes.

Collected data were entered in SPSS version 22. Descriptive analysis was done and a Chi-square test was used to observe the association of different variables with disease status and time in imprisonment. p-value <0.05 was considered statistically significant.

RESULTS

A total of 100 women prisoners were asked about their general health condition. It has been found that 70% of the respondent had no complaint of any disease, while 30% showed at least one sign or symptom. Most of the prisoners (61%) were less than or equal to 30 years of age. The majority (81%) of the inmates were not natives of Sindh compared to only 19%. Half of the participants (51%) were in prison for less than or equal to 6 months. A significant proportion (96%) of women prisoners were drinking tap water and (73%) responded that sanitary conditions in jail were satisfactory. Almost half of the prisoners (58%) were addicted to the pan, gutka, cigarette smoking, and even intravenous drug abuse. (Table 1)

Regarding the presence of different types of diseases, joint problems (34%) were the most frequently present among women prisoners, followed by hypertension (30%), skin problems (28%), allergic disorders (27%), respiratory problems (19%), psychotic illness (14%) and diabetes mellitus (11%). Statistically significant ($P < 0.05$) relationship has been found between hypertension and allergic disorders and time spent in prison (Table 2).

Table 1: Relation of different variables with disease status

Variable	Health Problems n = 30 (%)	Normal n = 70 (%)	Total n = 100	p-value
Age (years)				
Mean ± SD (31 ± 11)				
≤30	14 (46.7)	47 (67.1)	61	0.074
>30	16 (53.3)	23 (32.9)	39	
Residence				
Sindh	26 (86.7)	55 (78.6)	19	0.415
Punjab	4 (13.3)	15 (21.4)	81	
Time since imprisonment				
≤ 6 months	15 (50)	36 (51.4)	51	0.999
> 6 months	15 (50)	34 (48.6)	49	
Type of Drinking Water				
Tap	28 (93.3)	68 (97.1)	96	0.581
Mineral	2 (6.7)	2 (2.9)	4	
Sanitary Conditions				
Satisfactory	24 (80	49 (70)	73	0.338
Not Satisfactory	6 (20)	21 (30)	27	
Addiction				
Yes	20 (66.7)	38 (54.3)	58	0.277
No	10 (33.3)	32 (45.7)	42	
Delivery in Jail				
Yes	1 (3.3)	5 (7.1)	6	0.665
No	29 (96.7)	65 (92.9)	94	
Treatment facility in Jail				
Yes	21 (70)	61 (87.1)	82	0.05
No	9 (30)	9 (12.9)	18	

Table 2: Association of different diseases with time in prison

Disease	Time in prison ≤ 6 months n = 51	Time in prison > 6 months n = 49	Total n = 100	p-value
Hypertension				
Yes	22 (73.3%)	8 (26.7%)	30	0.004
No	29 (41.4%)	41(58.6%)	70	
Diabetes				
Yes	3 (27.3%)	8 (72.7%)	11	0.118
No	48 (53.9%)	41(46.1%)	89	
Respiratory Problem				
Yes	9 (47.4%)	10 (52.6%)	19	0.802
No	42 (51.9%)	39 (48.1%)	81	
Skin Problem				
Yes	8 (28.6%)	20 (71.4%)	28	0.007
No	43 (59.7%)	29 (40.3%)	72	
Joint Problem				
Yes	13 (38.2%)	21 (61.8%)	34	0.091
No	38 (57.6%)	28 (42.4%)	66	
Allergic disorder				
Yes	7 (25.9%)	20 (74.1%)	27	0.003
No	44 (60.3%)	29 (39.7%)	73	
Psychotic illness				
Yes	10 (71.4%)	4 (28.6%)	14	0.149
No	41 (47.7%)	45 (52.3%)	86	

DISCUSSION

This descriptive cross-sectional study was carried out to identify the general health condition among female inmates in Karachi prison. Almost every prison in Pakistan is inefficient in providing adequate accommodation for the prisoners as they are mostly overpopulated. Due to poor resource management, the old buildings are in miserable condition. Their dilapidated structures could be quite hazardous for the health of inmates.[12] This overcrowding is coupled with poor sanitary conditions which further worsen the health issues.[13,14] Most of the cells accommodated up to 30 inmates with a single toilet and poor sewerage system. Furthermore, this lack of space left the prisoners with no choice but to sleep on the floor posing detrimental health effects. To make the conditions worse, these prisons are also inhabited by the children in the same living conditions as their inmate's mothers. Some of these unfortunate children were given birth on the premises of the jail. The prevalence of deliveries within jail premises was found out to be just 6%.[15] The segregation in prisons violates human dignity and causes emotional torment for the female prisoners.[14] The rooms, originally built to accommodate not more than ten prisoners with moderately to severely affect hygienic conditions of living standards. Hence, the prisoners are exposed to multiple risk factors, increasing their vulnerability to a vast array of different diseases.[15]

In our study, 61% of the participants are equal to or less than 30 years of age. A study from Lahore reported that 48% of women in prisoners were below 30 years of age.[16] Sanitary conditions in prison are found satisfactory by 73% of the participants, however several other studies in Pakistan reported that sanitary conditions in prisons were pathetic and unsatisfactory.[17,18] Complete details of differentials of addictive behavior also need to be evaluated. More than half (58%) of the women prisoners were using different types of addictive substances. Studies found that drug addiction among women was on the rise in prisons of Pakistan.[12,19]

Different types of chronic diseases were also prevalent among women in prison. Due to sleeping on the floors and less exposure to sunlight, 34% of them were found to be experiencing joint problems. Mental dissatisfactions, confinement, and severely affected living standards have made them vulnerable to mental trauma with almost 14% affected with some kind of psychotic illness. The non-communicable diseases have emerged as a health crisis and are increasing globally. Mental stress and trauma in prisoners be being prone to hypertensive state. About 30% of the inmates are hypertensive and 11% diabetic. Similar findings are revealed from other studies reporting a high prevalence of hypertension, diabetes mellitus, musculoskeletal disorders, mental illness, and communicable diseases among women prisoners.[11,14,20] Another study in Karachi highlighted the high prevalence of hypertension among prisoners.[21] Statistically significant relation and the ship was observed between hypertension and allergic disorders among women prisoners and time since imprisonment (p-value <0.05)

Despite the availability of medical and treatment facilities, the inmates are still experiencing illness and the prevalence of diseases. It is of utmost importance to identify the cause of such disease prevalence and factors playing role in disease causation. In other words, a complete social autopsy of the disease patterns needs to be tracked down to identify the limitations of the health care delivery system which has failed to reduce the disease prevalence among the prison inmates. The limited number of participants, time constraints, and feelings of insecurity were among the limitations of this study.

CONCLUSION

The general health condition among female prisoners is unsatisfactory. Hypertension and allergic disorders are highly prevalent in women prisoners. Although the sanitary

condition is satisfactory, there were no proper arrangements of hygienic food and water, lack of ventilation, and overcrowding which predisposes these inmates to various health problems.

AUTHOR'S CONTRIBUTION

NM: Study design, Statistical analysis and Editing of manuscript
SMM: Data analysis, Interpretation, Editing and Final proofreading
NS: Data collection and Manuscript writing
SIAF: Data collection and Manuscript writing

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Review Article

DEADLY INFLAMMATORY CYTOKINE STORM AS IMMUNE RESPONSE IN COVID-19 PATIENTS

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ABSTRACT

Coronavirus disease 2019 (COVID-19) outbreak which is caused by infection with SARS-CoV-2 was declared as a massive threat to international health by WHO in March'2020. This SARS-CoV-2 infection leads to immune reactions in the host known as cytokine storm, dysregulation in the host immune system leading to uncontrolled release of cytokines. Several clinical studies emphasize pertinent changes occurring in both innate and adaptive immune systems of the human body in response to SARS-CoV-2. As the world must live amidst the current ongoing virus, understanding the immunology of the disease can assist in disease containment and the development of more effective vaccines and therapeutics to prevent and treat patients infected with COVID-19. Here, we have discussed the changes in the host immune response to infection by SARS-CoV-2, mechanism of cytokine storm & association of other major cytokines.

Key Words: SARS-CoV-2, COVID-19, Acute respiratory distress syndrome

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INTRODUCTION

Coronaviruses (CoV) are a class of viruses that specifically targets respiratory systems and belong to the coronaviridae family.[1] They have been reported to infect birds and mammals including humans and cause infections of the upper and lower respiratory tract and severe acute respiratory syndrome (SARS).[2] Based on genetic studies, coronaviruses have been categorized into three major groups' alpha, beta, and gamma-coronaviruses.[2] The primary host reservoir of alpha and beta-coronaviruses are reported to be bats and the analysis of alpha and beta-coronavirus genera was confirmed by their presence in wild mammals like bats, hedgehogs, rodents, and lagomorphs.[3] The SARS epidemic of the year 2003 witnessed 8096 cases in 25 countries and indicated the possible health threat by the transmission of Coronavirus (CoV) from bats to humans and by its ability to diversify through recombination rapidly.[4] Coronaviruses have also been reported to be the causative agents of some earlier respiratory linked outbreaks that include SARS-CoV and MERS-CoV. Later, in December 2019, an uncommon infectious disease spread among people from the wild animal and seafood market of Wuhan, China, with initial symptoms like pneumonia. A global emergency was declared immediately by the WHO due to the rapid transmission of this contagious disease as the number of cases reached an alarming stage with over 82,000 cases in 27 countries by February 2020.[5,6] By March 10, 2020, the disease further progressed to a pandemic with

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110,000 infectious cases and 4000 deaths globally.[7]

The disease caused by this novel coronavirus 2019 (SARS-CoV-2) was named COVID-19 by WHO in February 2020.[8,9] Among the coronavirus family, it is found to be the 7th severe disease-causing coronavirus that infects humans and is found to be the causative agent of COVID-19. The genomic studies of this virus show that SARS-CoV-2 is not intentionally manipulated and is not a lab-controlled virus instead it is a naturally occurring virus from the coronavirus family. SARS-CoV-2 shows 76.9 % genomic sequence similarity with SARS-CoV and is reported to be an enveloped RNA virus.[10]

The comparative study of SARS-CoV-2 with SARS and MERS coronavirus suggested its origin from beta coronavirus and also confirmed their structural similarity due to the presence of four common structural proteins (spike, nucleocapsid, membrane, envelope), other accessory proteins, and sixteen non-structural proteins as well. The spike protein (S) containing an S1 subunit and S2 subunit at N-terminal and C-terminal respectively aids receptor binding and membrane fusion of the virus with the cell. To get entry into the host cell, the (S) protein of SARS-CoV-2 requires an appropriate binding with the ACE2 receptor of the host. It has also been reported that the receptor-binding domains (RBD) of spike proteins of SARS-CoV and SARS-CoV-2 show homogenous binding affinities with the ACE2 receptor.[11] RBD of (S) protein consists of six amino-acid residues that are crucial for the binding of RBD with the receptor. Comparative analysis revealed that 5 of these amino acid residues differ in SARS-CoV-2 (S) protein as compared to that of SARS-CoV.[11]

The entrance of coronavirus into the host target cell has been reported to occur through endosomal-membrane fusion triggered through the binding of S-protein of SARS-CoV-2 with ACE2 receptor of the host cell.[12] The transference of virus-receptor complex to endosomes actuated the fusion activity along with the cleavage of S-protein by proteases.[13] After the internalization, N-protein is primarily involved in the formation of Nucleocapsid and localization to the endoplasmic reticulum (ER) thus assisting assemblage and budding also.[14] Membrane protein being the most abundant protein, was found to be associated with the maintenance of the shape of the virus, interaction of all proteins of CoV, the formation of the viral envelope, and the release of VLPs.[15] The smallest protein, E-protein, has been investigated to be important in the replication, production, and maturation of the virus and its high expression within infected cells.[16] Moreover, it has also shown its participation in the assembly and budding of CoV from the Golgi-ER complex.[16]

In this review article, we have summarized previous and recent advancements related to the immune responses elicited in the host by SARS-CoV-2 infection which leads to deadly inflammatory cytokine storm in COVID-19.

Innate immune responses generated by SARS-CoV-2 infection

The first line of defense mechanism that includes non-antigen specific and natural immediate response is referred to as innate immune response.[17] The induction of inflammatory immune response mediated by macrophages and granulocytes in SARS-CoV-2 infected lungs cells has been reported. The host recognition receptors that differentiate viral stuff from host material and start immune responses through their activation have been investigated to include TLR-7, RIG-1, MDA-5, and cGAS-STING pathways.[18] The activation of recognition receptors triggers the type-1 IFN and inflammatory cytokines expression which has been demonstrated to restrict replication of virus by the activation of IFN stimulated genes. Researchers reported that an early immune response of IFN restricts viral replication efficiently while a delayed IFN response stimulated cellular damage in older persons.[19] The blockade of interleukin-6 (IL-6), IL-1 and tumor necrosis factor (TNF) production has been reported to be beneficial

against cytokine-release syndrome in patients suffering from COVID-19.[20]

The comparison of SARS-CoV-2 patients with previous pneumonia patients had shown a high expression of chemokines (Hyper-cytokinemia) in SARS-CoV-2 patients and stimulated expression of IFN-stimulated genes as well as inflammation-causing genes.[21,22] Moreover, an increase of over-expressed neutrophils and dendritic cells has also been reported in SARS-CoV-2 individuals.[23] It had also been revealed through transcriptional profiling of COVID-19 patients that an unsuitable inflammatory response assisted by decreased levels of interferons and high levels of chemokines confirmed a diminished innate-antiviral immune response caused by SARS-CoV-2.[24,25] Innate immune responses elicited by SARS-CoV-2 have been demonstrated to include reduced type-1 IFN response, activated hyper-inflammatory response, elevated neutrophil, and macrophage and induced Th1 or Th17 expression at initial stages of the virus.[26] Like SARS-CoV, COVID-19 has also been reported to suppress type-1 IFN production at initial stages and its transmission in asymptomatic individuals revealed slowed early innate immune response by the host against SARS-CoV-2.[27] An increased production of IgG antibodies and development of a T-cell response eliminate infected cells in COVID-19 patients.[28,29] Innate immune pathways like STAT-1 and MyD88 have been observed to partially control the pathogenesis of SARS-CoV-2.[30] During a host innate immune response study, it has also been scrutinized by various studies that human lung epithelial cells of SARS-CoV cease to trigger dendritic cell maturation and MHC class 2 complex expression.[31] In a comparative study between young and old SARS-CoV infected mice, elevated expression of TNFA, IL-6, CCL-2, CCL-3 and CXCL-10 has been investigated.[32] SARS-CoV infected human alveolar cells have been investigated to exhibit elevated levels of interferon- β, interferon- λ, cytokines, and chemokines during an innate immune response.[33,34] A potent innate immune response depends on type-1 IFN responses and pathways that eliminate viral replication further trigger an active adaptive immune response.[35]

Adaptive immune response to infection by SARS-CoV-2

The generation of neutralizing antibodies in patients infected with SARS-CoV has been detected upon and after the onset of illness against the virus.[36] The CD4+ and CD8+ T-cells along with other memory T-cells have been investigated to protect the host against the virus.[37] The identification of SARS-CoV-2 specific CD4+ and CD8+ T-cells has been reported with the recognition of type 1 and 2 HLA peptides in infected patients.[38] The expression of the spike-1 immunoreactive protein of SARS-CoV-2 in targeted cells can display viral proteins or markers and thus help in the development of an immune response.[39] B and T-cell epitopes have been identified as the prominent targets for generating immune responses against COVID-19 infection.[40] The analysis of adaptive immune response in SARS-CoV immunized mice has been reported to show elevated levels of CD80, CD86, and MHC class 2 molecules on mice dendritic cells (CD11c+).[41] Elevated numbers of some anti-inflammatory cytokines like IL-37 and IL-38 has been reported to successfully inhibit inflammation, class-2 MHC molecules, MyD88 pathway, TNF, CCL2, and IL-1β in SARS-CoV-2.[42] Release of several cytokines and chemokines during innate immune response has been demonstrated to trigger the activation of some other immune cells like neutrophils, macrophages, and dendritic cells to start an adaptive immune response to fight against SARS-CoV. It has been investigated that down-regulating the expression of CD8+ T-cell function in microglia and astrocytes helped in the control of CoV viral replication and secretion of neutralizing antibodies, also prevented its re-appearance.[43] In the case of SARS-CoV, the reduced number of CD4+ T-cells have been observed to slow down the production of cytokines and neutralize antibodies thus, failing to remove the viral

infection.[44] The release of cytokines and chemokines upon viral entry has been reported to trigger the production of cytotoxic T-cells (CD8+) and helper T-cells (CD4+).[45]

Mechanism of cytokine storm and involved cytokines

The SARS-CoV-2 infection generates cytokine storm in the lung due to uncontrolled secretion of inflammatory cytokines at the site of infection by immune cells (T-lymphocytes, dendritic cells, monocytes, macrophages) in the lungs. These inflammatory cytokines further cause acute respiratory distress syndrome (ARDS). According to a report published in Lancet states that ARDS is a major death factor in patients suffering from COVID-19. It is an immunopathological event that occurs after MERS, SARS, and SARS-CoV-2 infections.[46] ARDS is correlated with cytokine storm because immune effectors cells have been observed to release a large number of chemokines i.e. CCL2, CCL3, CXCL8, etc. and pro-inflammatory cytokines including; IFN-γ, IL-1β, IL-6, TGFβ, granulocyte-macrophage colony-stimulating factor, interferon-gamma-induced protein, MCP-1, MIP-1α, MIP-1β, PDGFB, and VEGF, etc., which results in the uncontrolled systemic inflammatory response and higher number of leucocytes. ARDS leads to cytokine storms, damages lungs and other multiple organs of the body which leads to multiorgan exhaustion and finally to death in severe cases.[47,48]

Interleukins

Higher levels of IL-1 and IL-2 in the serum of COVID-19 individuals have been observed and its elevated levels are correlated with the severity of the disease. Some therapeutic strategies, including mesenchymal cells (MCS), and other immunomodulatory drugs for the inhibition of IL-1 are under trial. TNF-alpha and IL-1-beta are major stimulators of the IL-6. In COVID-19 patients T-cell dysfunctionality, compromising the capacity of T cells against pathogens has been reported. Increased IL-6 level is related to a poor prognosis of the disease. Clinicians observed that inverse proportionality between elevated IL-6 levels and leucocytes count exists among patients admitted to ICU. The level of IL- 6 was remarkably elevated in patients who died than those who recovered from COVID-19.[49-51] Elevated secretion of IL-7 increases the production of pro-inflammatory cytokines and has a negative regulatory effect on TGF-β. Clinical researchers have indicated that the IL-7 level in COVID-19 patients is directly related to the severity of the disease. IL-10 blocks the production of pro-inflammatory cytokines; IFN-γ, TNFα, and IL-1β in different cells and arrest the maturation of dendritic cells by inhibiting the function and pathway of IL-12. According to various reports, clinicians have detected higher levels of IL-10 in patients suffering from COVID-19.[52-54]

Interferon-gamma induced protein-10

IFN-γ induces the secretion of CXCL10 (IP-10) which starts recruitment of leukocytes in inflamed tissues after binding with chemokine receptor-3 which results in inflammation leading to the deterioration of tissues. Elevated IP-10 levels have been observed in viral infections. Similarly, higher levels of serum IP-10 levels have been observed in patients suffering from SARS-CoV-2 particularly in those who were required intensive care unit admission which causes damage to lungs and disease severity.[55]

Interferon-gamma

IFN-γ can cause common cold-like symptoms, fever, headaches, dizziness, and fatigue. Interferons are pivotal molecules that act as antiviral agents in the initial stages of infection. The delayed release of IFNs in primary stages of MERS and SARS-coronavirus infections, obstruct the antiviral response of the body's immune system against these viral infections. In serum of COVID-19 patients, IFN-γ levels were elevated and this may be due to the activation of helper T-cells (Th1 and Th2).[56,57]

CONCLUSION

The outbreak of SARS-CoV-2 infection and the nature of COVID-2019 has demanded swift action in both basic immunological science and clinical research. In response to this, the scientific community has met with remarkable productivity in finding out the immunopathology of COVID-19. Within months, clinicians have done various analyses to investigate the host-pathogen interaction and immunology of SARS-CoV-2 infections. The violent response to SARS-CoV-2 infection is the uncontrolled release of proinflammatory cytokines and chemokines which results in induction of apoptosis and necrosis in epithelial and endothelial cells of lungs further leading to multiple organs dysfunction. Clinical researchers have found that the changes in the levels of these cytokines indicate the severity of the disease and its unfavorable prognosis. All these deteriorating conditions give rise to ARDS and finally death. Current evidence on adaptive immune responses strongly suggests that T-cell responses are crucial for the control of SARS-CoV-2. The possible therapeutic approaches are required to inhibit these outcomes, which include the use of antivirals, immunomodulators, immunosuppressant agents, and vaccines reducing the mortality and morbidity rate of patients suffering from COVID-19. Precise projection and targeted intervention using suitable cytokine storm antagonists, during the COVID-19 infection will be essential to improve the survival rate among patients and further investigations are required to verify various drugs and available vaccines.

AUTHOR'S CONTRIBUTION

MSA: Article writing
MSQ: Conception of idea
ZK: Review critically
TH: Editing
KA: Editing
AA Editing

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Case Report

PRIMARY INTRATHORACIC PLEUROPULMONARY SYNOVIAL SARCOMA WITH RIB METASTASIS: A RARE ENTITY

Palwasha Gul[1], Pari Gul[2]

ABSTRACT

Primary synovial sarcoma is common in limbs, in para particular location. Lungs are commonly involved by metastatic sarcoma due to hematogenous spread whereas primary pulmonary synovial sarcoma in the lungs is an infrequent entity but highly aggressive. Symptoms and imaging findings are non-specific to make definite diagnosis, therefore it is easily confused with other pathologies. The key to correct diagnosis is histopathology.

Primary pleuropulmonary synovial sarcoma is extremely rare. It is important to excluded other sites of primary synovial sarcoma. We report 50 years old female who presented with cough and dyspnea. CT scan showed enhancing circumscribed mass in left hemithorax which proved to be synovial sarcoma on core biopsy.

Key Words: Synovial sarcoma, Lung, Metastasis

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INTRODUCTION

Synovial sarcoma (SS) constitutes 8% of all soft tissue tumors in the body. The term "synovial sarcoma" is a misnomer, as it arises from pluripotent mesenchymal tissue and not the synovial tissue as the name suggests. Its common presentation is in limbs, in para particular location, so it is mistakenly thought to originate from synovium. Common location is close to the large joints in 90% of the cases, however in 10% of the cases it can be seen at other locations such as lung, mediastinum, abdomen, head and neck and heart.[1, 2]

Primary pulmonary sarcomas in the lungs constitutes only 0.5% of all primary lung malignancies with only a few case reports in the literature. Primary SS in pleuropulmonary and mediastinal location has more aggressive course as compared to SS of the extremities.

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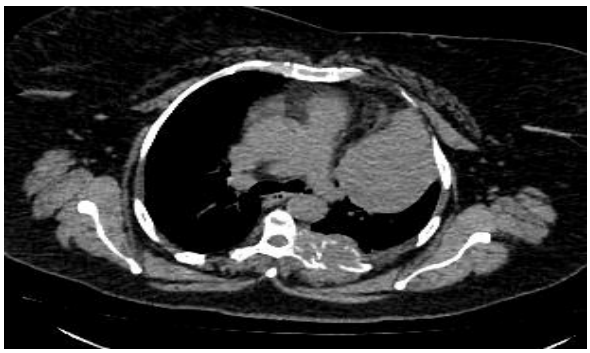
Multi-disciplinary approach is needed for correct diagnosis which includes clinical/ imaging findings, tissue sampling and immunohistochemical investigations to exclude alternate neoplasia and metastatic sarcoma.[2]

CASE REPORT

We present a case of 50 years old married female. She presented with cough and dyspnea. Her x-ray chest showed an opacity in left upper lobe. Primary lung malignancy was concern of pulmonologist and radiologist therefore contrast enhanced CT was performed on 128 slicer Toshiba prime aquiline. CT scan showed circumscribed enhancing mass with smooth margins (Fig 1a, b, c). It showed broad interface with adjacent pleura. The mass was abutting left pulmonary artery and left sided cardiac chambers. Partial encasement of left upper lobe bronchus was also noted. No mediastinal lymph nodes were seen. There was destructive mass with soft tissue component in left posterior 5th rib (Fig 1 a, b). There was minimal left pleural effusion.

Radiology report gave possibility of lung mass with osseous metastasis and CT guided biopsy of the main mass and rib lesion was planned. In the meantime, clinical examination of the periphery and imaging of the abdomen and pelvis was also performed which was negative for primary malignancy / distant metastasis. Biopsy of lung mass was consistent with synovial sarcoma whereas rib lesion was consistent with its metastasis. Patient was referred to oncologist and thoracic surgeon for further management



a

b

c

Fig-1: Plain (a), post contrast (b) and lung window (c) from Contrast enhanced CT chest showing pleuropulmonary enhancing circumscribed mass in left upper lobe abutting left main pulmonary artery. Left 5th rib shows destructive lesion with enhancing soft tissue component

DISCUSSION

Primary pulmonary SS is a rare entity. The average age of onset for pleuropulmonary location is 38.5 years. Both genders are equally affected with similar predilection for right and left lungs.[2,3] Our patient was 50 years old female with mass in left upper lung. The secondary synovial sarcoma is frequent in lungs however primary is a rare entity. The primary tumor is usually seen in the soft tissues. Literature states that primary synovial sarcoma of the lungs mostly presents as a large pleural-based, inhomogeneous lesion.[1] Pleural effusion is reported, while mediastinal lymphadenopathy was infrequent.[2] In most cases of primary synovial sarcomas of the lung, the primary presentation is with chest pain, hemoptysis, cough, shortness of breath or ipsilateral pleural effusion. Our patient presented with cough and dyspnea. Streak of pleural effusion was also noted in our case on left side ipsilateral to the mass.

Essay and colleagues were first to suggest the term “pleuropulmonary” to describe the anatomic subtype of primary SS originating from either the lung or the pleura, as there were difficulties in defining the exact anatomic location in most cases. There is no large data defining the precise number of pleuropulmonary SS cases worldwide.[4]

Surgical resection is the treatment of choice, although chemotherapy and radiotherapy can also be used as an option. There is no standardized treatment for primary lung SS.[2]

The prognosis for patients with primary lung synovial sarcoma is poor, with an overall 5-year survival rate of 50 percent. Factors predicting a worse prognosis with synovial sarcomas include tumor size (>5 cm), male patients, older age (>20 years), extensive tumor necrosis, high grade, large number of mitotic figures (>10 per 10 hpf), neurovascular invasion, and recently, the *SYT-SSX1* variant.[5]

CONCLUSION

Primary synovial sarcomas although rare but can be encountered in clinical practice. It cannot be diagnosed or predicted radiologically as primary synovial sarcomas doesn't give any specific findings on imaging. However, imaging can play important role in assessing its size/ morphology and its metastasis. The key to correct diagnosis is histopathology as in our case.

Disclaimer: none

Ethical review committee: approved by hospital ethical committee (BMCH, Quetta).

AUTHOR'S CONTRIBUTION

PG: Data collection, Data analysis and Drafting
PG: Review critically

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