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EDITORIAL

ROLE OF PAKISTANI UNIVERSITIES IN COMBATING COVID-19

Muhammad Imran
PhD, Department of Biological Sciences, International Islamic University Islamabad
muhammad.phdbt108@iiu.edu.pk

In Pakistan, the total number of universities is 177 and more than 12,000 active Ph.D. faculty members are working. Approximately 1500 Ph.D. scholars are enrolled every year in different fields. Above mentioned statistics are the best indicators for a developing country such as Pakistan. After the COVID-19 outbreak, world scientists across the globe raced to develop drugs, instruments, personal protective equipment (PPEs), and vaccines to control outbreaks. In this situation, Pakistani scientists were involved in different projects which were related to the COVID-19 outbreak.

All universities done their best endeavor according to their existing resources in COVID-19. The University of Engineering and Technology(UET), Lahore researchers designed cost-effective personal hygiene articles and ventilators[1]. The expert research team of ASAB, NUST Islamabad claimed to establish a cheaper COVID-19 molecular-based diagnosis testing assay. This assay cost was 1/4th of the current market available price of the test. This historical achievement was done with the collaboration of the Wuhan Institute of virology China, the German center for infection Research (DZIF), the Armed Forces Institute of Pathology CMH Rawalpindi, and Columbia University USA[2].

Another exertion done by the Centre of Excellence in Molecular Biology; Punjab University Lahore scientists team to develop a cheaper diagnostic test assay for the detection of COVID-19, one test price was estimated up to Rs 800 (5 US dollars) only[3]. A breakthrough was noted in International Centre for Chemical and Biological Sciences (University of Karachi), which identified nine compounds that could inhibit the virus growth in the host cell. The aim of this project was to invent a viral protein functional inhibitor. At this university, the vaccine designing project was also launched[4].

The Punjab University, chemical engineers developed anti-viral disposable wipes and sanitizers according to the world health organization's (WHO) standard operating procedure (SOPS). Different sources of COVID-19 spread were reported, and wipes could be used for the decontamination process of different items such as purses, mobile phones, pens, keys, stair railings, ATMs, public washrooms and door handles[5].

The national university of science and technology is the state of art and leading institute in Pakistan. The CEME (NUST) researcher-developed bilanguage (English and Urdu) screening COVID-19 application. The name of the app was "COVID CHECK PAKISTAN", which was used for the screening process. In initial approximability, 8,000 people from different counties such as USA, UAE, Saudi Arabia and the UK were screened. This application was the first-world application in the Urdu language version, enabling screening of the Pakistani population easily due to the mother tongue software version[6].

Pakistani university's efforts were not hidden during the pandemic, as NUST Aga Khan University and Aga Khan University Hospital launched the "CoronaCheck "mobile applications enable to screen people easily and safely to evaluate symptoms, while staying at home. This application used an interactive chatbot, based on the Artificial Intelligence technique, which helps out Pakistani population users to understand COVID-19-related signs and symptoms and was helpful for intime treatment. Its basic aim was to identify potential COVID-19 carriers and limit its transmission risk. This app's best features included WHO guidelines, Urdu language videos, lists of government hospitals, and their helpline details. The concept of this app development was to reduce the burden on the healthcare system. The "CoronaCheck" App helped to tackle misconceptions and the bulk of unverified information on social media platforms having featured educational videos and were available on Google Play Store to download[7].

NUST, ASAB researcher achievement was to the sequenced complete genome of SARS-CoV2. This effort was to identify tracing the evolutionary origin of COVID-19 that infected the Pakistani population, is

useful for comparative genomic analysis. This discovery could play a vital role in accurate assay development and vaccine design. This project was completed with the collaboration of AFIP, Rawalpindi, and Charite-Berlin Germany and was published through National Genome Data Centre China, on March 25, 2020, was the first 29836 bp genome sequence using 2 isolates from Gilgit, Pakistan published from Pakistan, and available on the following link NCBI https://www.ncbi.nlm.nih.gov/nuccore/MT240479, GISAID, and NEXT RAIN[8].

The research team of the reputed national university located in Rawalpindi claimed that COVID-19 sequence, 2 isolates were taken from Manga, Pakistan. This data was published on April, 06, 2020. It was the 2nd 29836 bp genome sequence, and available on the following link NCBI: https://www.ncbi.nlm.nih.gov/nuccore/MT262993.1[9].

I conclude that the world had faced different pandemics like COVID-19 in different centuries. No doubt Pakistani government's planning, situation monitoring, coordination, disease assessment, and continuity of healthcare provision were excellent. The Government should launch different projects to handle crises and provide funding to the universities. Higher Education Commissions should promote excellence in research through various incentives.

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RESEARCH ARTICLE

MYTHS AND MISCONCEPTIONS RELATED TO COVID-19 VACCINATION AMONGST GENERAL PUBLIC OF ISLAMABAD AND RAWALPINDI

Farah Rashid[1], Nadia Junaid[2] , Ayesha Liaqat[3] , Bint i Hajra Zainnab[3], Bismah Ashraf [3], Adil Safdar[3]

[1] Professor of Community Medicine, Federal Medical College, Islamabad, Pakistan
[2] Assistant Professor of Community Medicine, Federal Medical College, Islamabad, Pakistan
[3] Student 4th Year MBBS, Federal Medical College, Islamabad, Pakistan

ABSTRACT

Objectives:

1. *To identify the myths and misconceptions regarding COVID-19 vaccination among the general public of Islamabad and Rawalpindi*
2. *To determine awareness regarding COVID-19 vaccination among the general public of Islamabad and Rawalpindi*

Design: *A Descriptive Cross-Sectional Study.*

Duration: *The study was carried out in the medical colleges and hospitals of Islamabad and Rawalpindi. It was a study of 8 weeks conducted between August and September 2021.*

Materials and Methods: *The study used both personal interviews and an online questionnaire. Google form having twenty-nine questions; each providing multiple choices in relation to the socio-demographic profile, vaccine status, myths and safety regarding the COVID-19 vaccine of the participants. One hundred and fifty three participants were included in the study. Participants were 18 years of age and above, residents of Rawalpindi and Islamabad. Individuals having any psychiatric disorders and cognitive disabilities and pregnant women were excluded from study.*

Results: *Our study revealed that 71(27.1%) of the respondents had no myths related to the COVID-19 vaccine. While 25(9.5%) believed that, the vaccine had active viruses and 18(6.9%) believed that the vaccine causes clots and varicose veins. Another myth was that the COVID-19 vaccine causes autism in children 4(1.5%).*

Conclusion: *The study revealed that the public residing in Islamabad and Rawalpindi had only a few misconceptions about the COVID-19 vaccination. The educated people had adequate knowledge with respect to the efficacy, effectiveness, and safety of the COVID-19 vaccines.*

Keywords: *COVID-19 vaccines, Pakistan, SARS-CoV-2, Vaccine Hesitancy, Vaccine Myths*

INTRODUCTION

In Wuhan, China, a couple of cases of pneumonia of unknown etiology were reported to WHO on the 31st of December 2019. In the coming month, after vigorous testing and scrutiny, the agent responsible for these cases was detected and termed as the Novel COVID-19. [1] The infection caused by this agent referred to as SARS-CoV2 and the illness inflicted given the name COVID-19.[1]

Correspondence:
Dr. Nadia Junaid
Community Medicine Department
Federal Medical College, Islamabad, Pakistan
Email: nadiajunaid@fmdc.edu.pk

On the 30th of January, the World Health Organization took notice of the alarming situation caused by this agent and declared this upsurge a "Public Health Emergency of International Concern". The World Health Organization labeled it as Corona Virus Disease 2019 (COVID-19) on 11th February 2020 and a pandemic on 11th March, 2020.[2]

Up till February 2021, one hundred and eight million people were affected worldwide, causing 2.38 million deaths. In Pakistan, 5,60,000 cases and 12,218 deaths have been reported.[3,4]

Coronavirus infection is zoonotic disease spreading infection among animals and humans. The illness

spreads through respiratory secretions, droplet transmission and contact transmission. [5]

Symptoms and clinical signs vary from mild fever and upper respiratory symptoms to serious pneumonia. Common side effects include migraine, loss of smell and taste, nasal blockage, runny nose, muscle, joint pains, exhaustion, abdominal cramps and diarrhoea.[6,7]

Worldwide four variants of SARS-CoV-2 recognized until mid-year 2021, these included Variants being monitored (VBM), Variant of interest (VOI), Variant of Concern (VOC) and Variant of high consequence (VOHC). [8]

In order to control the continuous spreading of COVID-19 pandemic, the most important step is the availability and accessibility of effective vaccines. In phase III trials various COVID-19 vaccines have been found to have efficacy as high as 95% in preventing symptomatic COVID-19 infections. Forty vaccines have been authorized by a national regulatory authority for public use.[9]

The assembly and utilization of adequate SARS-COV-2 immunization faces many difficulties, choosing a suitable formulation, approval, mass manufacturing, cost issues and distribution. Alongside significant hurdle to legitimate immunization, there is vaccine reluctance among the population.[10]

Vaccine hesitancy refers to a delay in acceptance or refusal of vaccination despite the availability of vaccination services. It is one of the most important barriers in execution of effective and mass vaccination. It can be related to three things i.e., confidence, convenience and complacency.[11] An absence of trust in antibodies and suppliers, smugness for the need for vaccination and vaccine cost and inaccessibility pave the way for vaccine hesitancy. Furthermore, personal, cultural, religious and psychosocial beliefs also lead toward reluctance to vaccination.[12] Moreover, conspiracy theories and beliefs add fuel to fire in further convincing individuals to go anti vaccine, these adversely affect the human behavior and strengthen their suspicion of governments, healthcare professionals and pharmaceutical industries. There are various myths regarding COVID-19 vaccination among the general population. Some most prevalent is, vaccines alter DNA, they aren't safe because of being newly prepared, safety is not established, unsafe in pregnant ladies, infertility in women and impotency in males[13], vaccines are developed just to control the population, vaccines cause autism, they contain mercury and various dangerous elements as their ingredients.[14]

In this paper we have assessed various myths and conspiracies prevalent among general public of Rawalpindi and Islamabad.

METHODOLOGY:

A descriptive study of cross-sectional type was carried out on patients visiting outdoor departments, (OPD) of different hospitals in Islamabad and Rawalpindi from 10th August to 20th September 2021, after the ethical review board of the institution granted authorization. Altogether, 153 participants was included in the study; selected through Non-probability convenience sampling. The inclusion criteria were individuals 18 years and above and residents of Rawalpindi and Islamabad. Individuals having any cognitive disorders, mentally impaired, pregnant ladies and psychiatric patients were excluded. People whose responses were recorded had been explained the objectives of the study. Informed consent was taken from everyone who participated. The participants were assured of the confidentiality of their responses. A questionnaire was developed in the English language containing 29 items after utilizing the information already accessible on the COVID-19 vaccine from published journals, public views and concerns. Questionnaire was divided into 3 sections; the first section dealt with the socioeconomic profile of the participant and contained 7 questions. The second section was dedicated to the vaccine status of the individual and it had seven questions in it. The third section had a total of 16 statements that tested the individual's knowledge of myths and safety regarding COVID vaccine.

A self-structured Questionnaire was distributed in 2 forms to the general public of Rawalpindi and Islamabad. An E-form in the shape of a “Google Form” was shared among individuals through online platforms that included WhatsApp, Telegram, Email and Facebook. Secondly, local individuals that could not interpret the English language were verbally explained the contents of the form and their answers recorded.

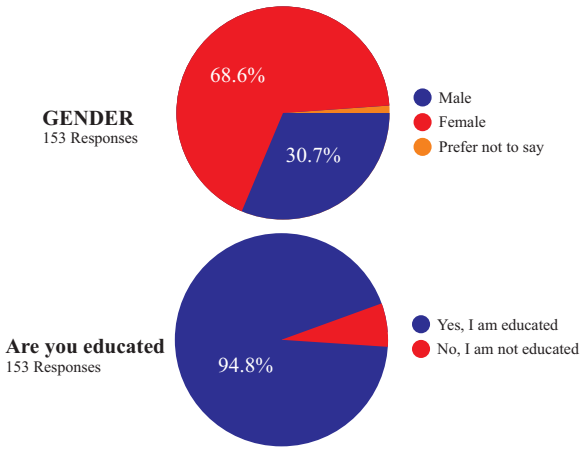
Participants duly filled out online questionnaires were included and incomplete forms were excluded from the study. Data were analyzed in SPSS version 25. Mainly descriptive statistics have been reported. For inferential statistics, we utilized the chi-square testing mechanism to assess the categorical variables where a p-value of < 0.05 was taken to be statistically significant.

RESULTS

Tables I, II and III show the demographic characteristics, vaccine status and myths status regarding COVID vaccine.

Table I: Sociodemographic characteristics of respondents

Characteristics	Number (n)	Percentage(%)
Age		
18-20	36	23.5
21-26	102	66.6
27-32	4	2.6
39 and above	8	5.2
Gender		
Female	105	68.6
Male	47	30.7
Prefer not to say	1	0.7
Martial Status		
Single	133	86.9
Married	18	11.8
Divorced	2	1.3
Residential City		
Rawalpindi	59	38.6
Islamabad	94	61.4
Educational Status		
Educated	145	94.8
Uneducated	8	5.2
Educational Level		
Under matric	3	2
Matric	1	0.7
F.Sc/F.A/I.com	18	11.8
Graduation	108	70.6
Masters	14	9.2
Monthly Income		
Upto Rs. 15000/-	60	39.2
Rs. 15001 – Rs. 30000/-	11	7.2
Rs. 30001 – Rs. 50000	18	11.8
Rs. 50000 and above	64	41.8



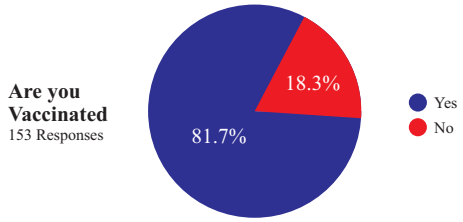


Table I represents the socio demographic characteristic of respondents. A total of 153 individuals responded, 30.7%(47) were male while the rest 68.6%(105) were females. The age distribution was made up of the following: 18-20(23.5%); 21-26 (66.6%); 27-32(2.6%); 33-38 (1.9%), and 39 years and above representing 5.2%. The majority of respondents were having graduation education (70.6%) followed by those with F.Sc / FA / I.com education (11.8%). The least being under matric education (2%). 61.4% (94) resided in Islamabad and the remaining 38.6%(59) lived in Rawalpindi.

Table II: Vaccine Status

Characteristics	Number (n)	Percentage(%)
Vaccine Status		
Vaccinated	125	81.7
Unvaccinated	28	18.3
Willingness to vaccinate (for unvaccinated)		
Willing	23	82.14
Unwilling	5	17.81
Reason of not getting vaccinated		
Mistrust in government	3	10.71
Lack of knowledge	3	10.71
Fear of side effect	10	35.71
Fear of injection	3	10.71
Accessibility	9	32.14
Vaccine Effectiveness		
Yes	130	85
No	19	12.4
Do not know	4	2.6
Vaccine Safety		
Yes	131	85.6
No	20	13.1
Do not know	2	1.3
Vaccine Control in pandemic		
Yes	127	83
No	20	13.1
Don't know	6	3.9
Vaccine role in controlling flu and pneumonia		
Yes	27	17.6
No	120	78.4
Don't Know	6	3.9

Table II shows the vaccine status of the participants. The majority of the participants were already vaccinated (81.7%), and the rest were unvaccinated (18.3%). Of those who were unvaccinated, (82.14) showed a willingness to get the vaccine. The most voted reason for not getting the vaccine was the fear of side effects (35.71%), followed by accessibility issues (32.14%). The majority (85%) believed in the effectiveness and safety of the covid vaccine. Eighty-three percent believed that vaccines played a role in the control of the pandemic and 27% believed that the covid vaccine could be used to treat flu and pneumonia.

Table III: Myths and safety regarding Covid Vaccine

Myths	Number (n)	Percentage(%)
1. Covid 19 vaccine causes infertility/impotency	14	5.3
2. Covid 19 vaccine is being used as a method of population control	16	6.1
3. Covid 19 vaccine alters DNA	15	5.7
4. Covid 19 vaccine causes autism in children	4	1.5
5. Covid 19 vaccine contains active viruses	25	9.5
6. Covid 19 vaccine contains controversial/ harmful substances	10	3.8
7. Covid 19 vaccine contains tracing devices/microchips	4	1.5
8. Covid 19 vaccine will cause death within 2 years	4	1.5
9. Covid 19 vaccine is pharmaceutical companies monopoly	12	4.6
10. Covid 19 vaccine clinical trail are only being used to make money	13	5
11. Covid 19 vaccine is being used by government to gather donations	21	8
12. Covid 19 vaccine will exacerbate my existing illness	11	4.2
13. Covid 19 vaccine is unsafe because its development was rushed	13	5
14. Covid 19 vaccine causes myocarditis	11	4.2
15. Covid 19 vaccine causes clots/varicose veins	18	6.9
16. I don't have any myths regarding the covid vaccine	71	27.1

Table III shows that the majority of the respondents had no myths regarding the covid vaccine (27.1%). The second majority (9.5%) believed that the vaccine had active viruses and after that (6.9%) believed that the vaccine causes clots/varicose veins. The least believed myth was that covid vaccine causes autism in children (1.5%).

Inference via CHI SQUARE TEST

Gender * I don't have any myths regarding covid vaccine Crosstabulation

Count

		I don't have any myths regarding the covid vaccine		Total
		Yes	No	
Gender	Prefer not to say	1	0	1
	Male	24	23	47
	Female	46	59	105
Total		71	82	153

Gender * Covid 19 Vaccine contains active viruses ? Crosstabulation

Count

		* Covid 19 vaccine contains active viruses		Total
		Yes	No	
Gender	Prefer not to say	0	1	1
	Male	9	38	47
	Female	16	89	105
Total		25	128	153

Are you educated? * I don't have any myths regarding the covid vaccine Crosstabulation

Count

		I don't have any myths regarding the covid vaccine		Total
		Yes	No	
Are you educated	Yes, I am educated	71	74	145
	No, I am not educated	0	8	8
Total		71	82	153

Chisquare test was applied to check association between myths regarding covid vaccines and gender and education

Association between myths and education level is significant p-value, is 0.42 at p-value < 0.05. Association between myths and age was also calculated by applying chi square test and association is not signifiant, p-value 0.54 as p-value > 0.5.

DISCUSSION

In our current study, we aimed towards investigating views of the public of Rawalpindi and Islamabad regarding the COVID-19 vaccine, particularly in terms of availability, acceptance, myths, and misconceptions prevalent in the local community.

Vaccine acceptance has remained a global challenge, especially in developing countries. Studies indicated various myths and conspiracies related to measles, mumps, rubella and polio vaccines that result in vaccine rejection. Pakistan had been facing the same issues with polio vaccines for decades. Addressing these myths and misconceptions is important to protect everyone.[14,15]

The results of our study disclosed that majority of the people are aware of the effectiveness and efficacy of the vaccine in controlling pandemics. People have adequate knowledge that vaccines are safe and necessary to halt the spread of disease. Especially, educated participants were more in favor of pandemic control through vaccination and most of them were against the misconceptions related to vaccines. Similar studies have been carried out in Canada, the US and other countries related to beliefs in vaccines associated with education level where characteristics such as socio-economic and education level are kept under consideration while evaluating candidates who have refused vaccination. [17, 18]

Among the very few myths identified, the beliefs that vaccines contain active viruses and that it is being used by the government to gather donations, were more prevalent. People also feared that the vaccine causes clots/varicose veins. Similarly, a few of the participants believed that vaccine is being used as a method of population control and may exacerbate the existing illnesses of the people. These findings are comparable with some studies in Sindh and Punjab which also stated that people feared vaccine safety because of its serious side effects. A similar study was also conducted in various districts of Sindh revealing the conspiracies and myths related to COVID-19 vaccines. [18]

This study has some limitations. Firstly, the sampling technique used is non-probability convenience sampling, making the results less reliable. Secondly, a study is limited to the twin cities of Islamabad and Rawalpindi. A nationwide study may be conducted for more comprehensive results.

Addressing these myths and misconceptions can surely help in changing the behavior of the people towards vaccination campaigns. People should be informed that the vaccines that do contain SARS-CoV-2, have undergone specific chemical treatments that inactivate the virus mostly by binding to the virus's genetic material inhibiting its replication, thus destroying its ability to cause COVID-19.[19]

Secondly, there is no solid conclusion that all COVID-19 vaccines cause blood clots. A few reports were obtained about the emergence of blood clots with AstraZeneca COVID-19 vaccine, but it has a 1 in 1000,000 chance of causing blood clots. And, in nations where the AstraZeneca vaccine has been widely used, but the overall rate of blood clots has not increased, indicating that the advantages of immunization clearly outweigh the hazards in many situations. [20]

CONCLUSION:

The study revealed that people had only a few misconceptions about the COVID-19 vaccination. The educated people had adequate knowledge with respect to the efficacy, effectiveness, and safety of the available corona vaccines. Health authorities and organizations should focus on proper awareness and counseling people regarding the safety of vaccines.

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RESEARCH ARTICLE

MACROTRABECULAR MASSIVE HEPATOCELLULAR CARCINOMA (MTM-HCC): A RECENTLY DESCRIBED HISTOLOGICAL SUBTYPE WITH CLINICAL IMPLICATIONS

Fatima Anwar, Zujajah Hameed, Zafar Ali, Faiza Hanif, Imran Nazir Ahmad

Department of Histopathology, Shifa International Hospital Ltd, Islamabad, Pakistan

ABSTRACT

Aim: *Macrotrabecular Massive Hepatocellular Carcinoma (MTM-HCC) is one of the newly described aggressive morphological variants of HCC. The aim of this study was to determine the frequency of MTM-HCC and to evaluate its clinicopathological significance.*

Material & Methods: *We conducted this retrospective study in our institute. The cases were retrieved and reviewed by pathologists to look for this variant. Cases were correlated with tumor size, serum alpha fetoprotein levels, cirrhosis, lymphovascular invasion (LVI), pathological grade and stage. Data were analyzed on SPSS version 22.*

Results: *MTM-HCC pattern was identified in 16.1% of the cases. Correlation between MTM HCC and histological grade (p=0.048), Lymphovascular invasion (p=0.005) and AFP levels (p=0.015) were found to be statistically significant.*

Conclusion: *Our study showed that the MTM-HCC subtype represents an aggressive form of HCC that may require more specific therapeutic strategies.*

Keywords: *Alpha fetoprotein, Hepatocellular carcinoma (HCC), Hepatitis B virus infection, Hepatitis C virus infection, Macrotrabecular massive.*

INTRODUCTION

Hepatocellular Carcinoma (HCC) is the sixth most common cancer and a fourth leading cause of cancer death worldwide[1]. Hepatitis B and C viral infections are the most common causes of HCC in underdeveloped countries, accounting for up to 32% of cases[2,3]. Other possible causes include smoking, alcohol and nonalcoholic fatty liver disease. HCC has a wide spectrum of histological patterns, common being solid, pseudo glandular and trabecular. Recently, in the 5th edition of the World health organization (WHO) Classification of Digestive System Tumors, certain distinctive histological patterns were described which are important to recognize due to their prognostic significance[4]. These include clear cell, lymphocyte rich, fibrolamellar, steatohepatitic, scirrhous and macrotrabecular massive (MTM-HCC). WHO has defined macrotrabecular pattern as trabeculae of hepatocytes more than or equal to 10 cells thick involving more than 50% of the entire tumor[5]. Studies have shown MTM-HCC has distinct molecular features and is associated with aggressive clinical behavior and poor prognosis. The aim of this study was to determine the frequency of MTM-HCC and to evaluate its clinicopathological significance.

Correspondence:
Dr. Zafar Ali
Department of Histopathology, Shifa International Hospital Ltd, Islamabad
Email: zafarali82@gmail.com

MATERIAL AND METHODS

This study was conducted after taking approval from Institutional Review Board and Ethics Committee. All resection specimens of HCC cases diagnosed at Shifa International Hospital between January 2018 to December 2019 were retrieved from the archives and reviewed for the presence of macrotrabecular massive pattern by a consultant histopathologist. All cases showing > 50% growth of macrotrabecular pattern ($\geq$ 6 - 10 cells thick) as per WHO criteria were categorized as MTM-HCC (Figures 1 & 2). Histological grade, lymphovascular invasion and pathologic stage were also evaluated and correlated. Serum alpha protein levels (AFP) of the individual cases were retrieved from each patient's electronic medical record and stratified into 3

groups. These groups were; those having normal range AFP levels (<10 ng/ml), slightly raised (10-100 ng/ml) and markedly raised (>100 ng/ml). Suboptimal core biopsies and cases in which other parameters, such as serum AFP levels, were not available were excluded from the study. Statistical analysis was performed using the SPSS version 22. Chisquare test was applied for correlation. Significance was defined as p value of < 0.05.

RESULTS

A total of 92 HCC cases were included. Out of these, 78 cases were male and 14 were female (M: F is 5.5:1). Age range was 35-76 years (mean age 54.4 years). The mean tumor size was 4.3cm. MTM-HCC pattern was identified in 15 cases (16.3%) (Figure 1). LVI (Lymphovascular invasion) was present in overall 39 cases (42.4%), out of these 20% cases were of MTM-HCC. The most common etiology of HCC was Hepatitis C (54.3%) followed by Hepatitis B infection. (Figure 2) Correlation between MTM HCC and histological grade (p=0.048), Lymphovascular invasion (p=0.005) and AFP levels (p=0.015) were found to be statistically significant. (Table 1)

HCC is one of the common cancers occurring worldwide and the commonest cause of primary liver cancers. It has a high propensity for recurrence, distant metastasis and chemoresistance. In the latest 5th edition of the World Health Organization (WHO) Classification of Digestive System Tumors, several histological subtypes have been described[5]. The significance of these subtypes is validated by their clinical relevance and genetic makeup. Among these subtypes, a novel and distinct subtype of HCC defined by the histological pattern of tumor cells is MTM-HCC.

MTM-HCC was recognized as a distinct pattern in 1983 and was suggested to represent a subtype of HCC, but due to lack of supporting studies, it was not until recently recognized as a separate subtype[7]. We followed WHO criteria of defining MTM-HCC which is the presence of macrotrabeculae of more than 10 cells thick in >50% of sampled tumor. This cutoff was similar to a study by Tan et al[9]. In contrast, studies conducted by Ziol et al and Jeon et al, MTM pattern was defined as the presence of macrotrabeculae of more than 6 cells thick in >50% of the tumor[6,9].

In our study, MTHCC constituted 16% of all HCCs as compared to 12% in the study by Ziol et al[3]. MTHCCs showed a male predominance similar to studies by Ziol and Jeon[6,10]. The mean age at diagnosis is 54 years. In contrast with Ziol, our study revealed slightly larger tumors in the MT-HCC subtype i.e 4.3 cm compared with Conventional HCC[6]. Similar to the findings of Ziol and Jeon, MT-HCC was more frequently observed in the context of viral hepatitis than with non-viral etiologies[6,10]. MTM-HCC exhibited a higher histological grade and tumour stage than CV-HCC.

In the review article by Calderaro et al he broadly classified HCC into proliferative and non-proliferative categories each carrying characteristic oncogenic pathway[11]. Among the proliferative types, MTM HCC is the distinct novel morphological pattern and their gene expression profiling revealed a unique gene expression related to neoangiogenesis causing over activation of angiopoietin 2 and Vascular Endothelial Growth Factor-A [VEGFA][11]. The association between negative biological and pathological criteria including high serum AFP serum levels, bigger tumour growth, vascular invasion and satellite nodules are most likely caused by underlying genetic disorders. Ziol and colleagues also demonstrated this connection[6].

In our study p-value was found to be statistically significant for tumor stage, vascular invasion and AFP levels. One important point to emphasize is that hepatocellular carcinomas are usually diagnosed on radiology and liver biopsy are not routinely done in every case. But now considering the importance of this pattern in this era of developing personalized medicine question on biopsy of every case arises so as to predict the natural course of the disease and to separate the potentially aggressive variant[12].

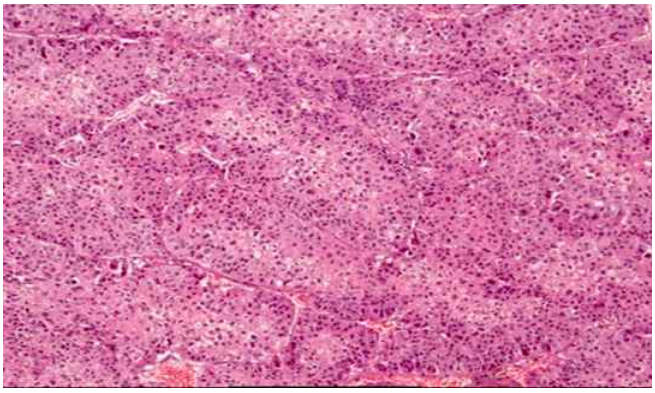

Figure 1: Macrotrabecular pattern of Hepatocellular Carcinoma showing thick trabeculae with more than 6-10 cell thick Hepatic plate (Hematoxylin & eosin stain, 10x magnification).

Table 1: Clinicopathological characteristics of MTM-HCC vs Conventional HCC (non MTM pattern)

	MTM-pattern	Non MTM-pattern	p-value
Sex	M:F 6.5:1	M:F 5.4:1	-
Age (y) mean	55	50	-
Size (cm) [%]	Upto 5cm (60) ➢5cm (40)	Upto 5cm (74) ➢5cm (26)	0.2
AFP levels (>100ng/ml) (%)	46	14	***0.015***
Stage (%)	pT1 (40) pT2 (33) pT3 (27) pT4 (0)	pT1 (39) pT2 (39) pT3 (13) pT4 (9)	*0.5*
Histologic Grade (%)	G1 (0) G2 (60) G3 (40)	G1 (7) G2 (79) G3 (14)	***0.04***
Lymphovascular invasion (%)	80	67	***0.005***

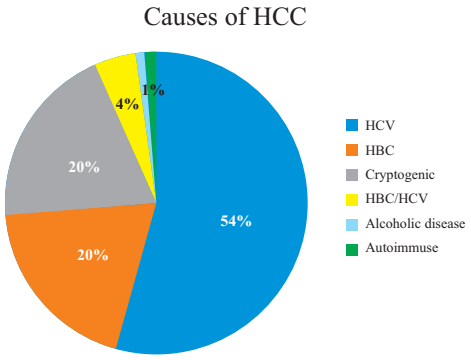

Figure 2: Different causes of Hepatocellular Carcinoma in our population. Hepatitis C viral infection being the most common cause, followed by Hepatitis B viral infections and cryptogenic causes.

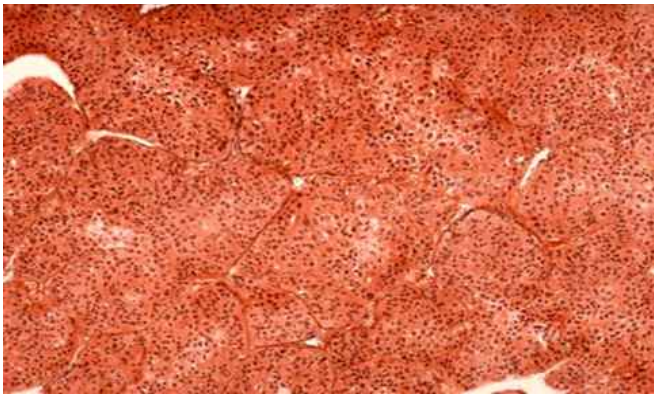

Figure 3: Special stain Reticulin highlighting thickened hepatic plate. These thickened plates contain more than 10 cells thick tumor cells which is consistent with Macrotrabecular pattern (Reticulin stain, 10x magnification).

CONCLUSION

Our results suggest that MTM-HCC is an aggressive version of HCC and therefore may require more intensive therapy.

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RESEARCH ARTICLE

COMPARISON OF CLOSED VS OPEN INTERLOCKING NAILING OF FEMUR IN TERMS OF DURATION OF SURGERY AND RATE OF INFECTION

Raja Adnan Ashraf[1], Kamran Asghar[2], Ahmed Javed[3], Sohail Iqbal Sheikh[4]
Syed Moosa Haider[5], Muhammad Salim[6]

[1] Assistant Professor, Department of Orthpaedics, Pakistan Railway General Hospital, Rawalpindi, Pakistan
[2] Assistant Professor, Department of Orthopaedics, Fauji Foundation Hospital Rawalpindi, Pakistan
[3] Medical Officer, Department of Orthopaedics, Pakistan Railway General Hospital, Rawalpindi, Pakistan
[4] Professor, Department of Orthopaedics, Pakistan Railway General Hospital, Rawalpindi, Pakistan
[5] House Officer, Department of Orthopaedics, Pakistan Railway General Hospital, Rawalpindi, Pakistan
[6] Professor, Department of Orthopaedics, Fauji Foundation Hospital Rawalpindi, Pakistan

ABSTRACT

Objective: *To compare the duration of surgery and frequency of infection in closed vs open interlocking nailing of femoral fractures.*

Study design: *comparative quasi-experimental study*

Place and duration: *The study took place from 10th October 2021 to 10th April 2022 in the admitted patients of the orthopedics department, Pakistan Railway General Hospital, Rawalpindi.*

Methodology: *Out of 80 patients, 40 were managed using a closed technique and the other 40 were treated with open surgery. It was approved from the college ethics committee. Femur fractures were classified using Winquist Hansen criteria and were managed respectively. Postoperative radiographs were obtained and OPD follow-ups were done at 06 weeks. The patients were evaluated for post-operative infections and followed further by phone calls.*

Results: *Thirty five percent (n=28) of the patients were female while 65% (n=52) male, 5% (n=4) of the patients got infected, 3 had had open surgery and 1 was managed using closed technique. The mean duration of surgery using closed technique interlocking nail was 160.5 minutes (120 to 180 minutes) while that of open interlocking nail surgery was 84.05 minutes (65 to 105 minutes).*

Conclusion: *The closed technique interlocking nailing of femoral shaft fractures is preferred due to a lower infection rate and less morbidity. However, due to non-availability of fluoroscope, open surgical technique for interlocking nailing is superior.*

Keywords: *Closed Nailing, Femur Fracture, Intramedullary Nailing*

INTRODUCTION

Femoral shaft fractures are the most common long bone fractures.[1] One-1.33 of 10,000 people per year present with femoral shaft fractures.2 In extremes of ages however, under 25 and older than 65 years, the incidence is found to be 3 per 10,000 people annually.[3,4] The injuries are usually associated with road traffic accident and gunshot wounds.[1,5,6,7,10] 30 working days are lost from a person's life on an average.[8]

Correspondence:
Dr. Kamran Asghar
Department of Orthopaedics
Fauji Foundation Hospital, Rawalpindi
Email: drkamranasghar@gmail.com

Most are managed using open techniques due to less chances of malunion.[9] Intramedullary nailing are standardized procedure for fixation of femur fractures.[10] During open surgery techniques, the fracture site is often repaired using retrograde intramedullary nailing. Closed techniques can be used as well for the management of femur fracture especially when associated with trochanteric fractures.[11] Closed technique intramedullary nailing is particularly useful for managing delayed fractures of the femoral shaft because they provide better control of limb length and circulatory stabilization.[12,13] We aimed to compare the differences in open and closed techniques and determine which technique is superior.

METHODOLOGY

We conducted a quasi-experimental study from the 10th of September 2021 to 10th of April 2022 in indoor patients of the orthopedics department of Pakistan Railway General Hospital, Rawalpindi. Patients from the ages 15 to 60 with femur fractures were admitted through the Accidents and Emergency department of Pakistan Railway General Hospital, Rawalpindi. Each patient was then evaluated using careful history taking, examinations and radiography. Inclusion criteria included closed fracture of shaft of femur, ages 15-60, and patients consenting to be part of the study, while those who had open fractures, were minors, elderly or did not consent were not included. Only traumatic fractures were considered for our study while pathological were excluded. Patients were then allocated into two groups, A and B, randomly by the lottery method after obtaining written informed consents.

Group A patients were managed using interlocking intramedullary nail through closed technique without opening the fracture site under the guidance of an image intensifier. Group B patients were managed by open technique. The operations were performed by a designated team of orthopedic surgeons under spinal anesthesia. The durations of the surgery were kept under strict observations.

Patients were discharged after 48 hours with oral antibiotics for seven days and followed up in the OPD after two weeks for stitch removal. A second follow-up was done at six weeks using clinical and radiological assessment to check for union and any evidence of infection. The final follow-up was conducted 12 weeks after surgery.

Data was analyzed using SPSS. Frequencies, percentages, mean and standard deviation, were calculated separately. P-value was considered significant at < 0.05.

RESULTS

All patients (n=80) were divided into two equal groups of 40 patients each. Sixty five percent (n=52) of the patients were male, and 35% (n=28) females, 5% (n=4) patients developed infections, out of which 3 were managed using open and 1 with closed technique as shown in Table I.

Mean duration for closed interlocking nailing was 160.50 minutes (range 120 to 180 minutes) with a standard deviation of 11.682. Meanwhile the mean duration for open interlocking nailing of femoral shaft fracture was 84.05 minutes (range 65 to 105 minutes) with a standard deviation of 8.265 as shown in Table II.

TABLE I: Frequency of infections

		Frequency	Percent	Valid Percent	Cumulative Percent
	Yes	4	5.0	5.0	5.0
	No	72	95.0	95.0	100.0
	Total	80	100.0	100.0	

TABLE II: Duration of surgery (minutes)

Type of surgery	Mean	N	Std. Deviation
Open	84.05	40	8.265
Closed	160.5	40	11.682
Total	124.60	80	40.365

DISCUSSION

Femur is a commonly fractured long bone. Different techniques of managing femoral shaft fractures have been suggested.[9] Closed techniques were developed after the invention of image intensifier. Unfortunately, in third world countries image intensifiers and great surgical expertise are not readily available therefore, open nailing with proximal and distal locking should be considered a superior priority. During open surgical technique, specially designed instrument used for proximal locking screw and different crude techniques like jigs, open the distal locking screw site and drill multiple holes to identify the site for distal locking screw used that increase the surgical time significantly.

Deep tissue infections with either technique, are a major hurdle in the complete recovery of patients. Infection rates are slightly higher in open surgery however, studies report similar infection rates with open reduction with intramedullary fixation and closed technique interlocking nailing.[13] The risk of infections is directly related to the extent of stripping of soft tissue and debridement, medullary canal reaming and irrigation, and the level of contamination.[16,17] Attempts to minimize soft tissue stripping were made and the area washed with great amounts of normal saline after reduction.

Preoperative antibiotics with sterile and good operative techniques are essential.[14,15] We gave preoperative antibiotics cefazolin 1 g to both groups. We reported infection in 1 patient managed with closed technique and 3 managed with open techniques 1.25% and 3.75%

respectively. The number of people in the operation theatre were also limited to prevent the chances of post-operative infections.

The duration of surgery is a vital parameter of measuring effectiveness of management. The mean operative time for closed techniques was 113.2 minutes with a standard deviation of 34.725 while that for open reduction was 132 minutes with a standard deviation of 35.670 minutes according to a study.[18] Our initial operative time was longer but with the course of this study it was shortened due to experience with the techniques. Mean time for open surgery in our study was 160.56 minutes (120 to 180 minutes) and 84.05 minutes (range from 65 to 105minutes) for closed method.

Achieving reduction both anteroposterior and lateral views during closed technique is difficult, however, essential. Both segments of the distal proximal fracture can be replaced with the help of a T-shaped end of the hand connectors. In some cases, a pin with a small diameter can be used to treat the nearest part of the fracture during the descent. These guidelines were used while deploying the closed technique during our study.

Salawu et el. reported that open surgery had lower complication rates however we observed less infection rates with closed techniques.[19] Ensuring good traction is pivotal during reduction in both techniques and prevents from angular deformities.[20] We did not observe any angular deformities in our study.

Limitations:

Even though we ensured uniformity of the staff the time of surgeries varied due to experience in techniques over time and external variables like temperature, microbiome, surgical devices and implants could not be uniformed.

CONCLUSION

The closed technique interlocking nailing of femoral shaft fractures is preferred due to a lower infection rate and less morbidity. However, due to non-availability of fluoroscope, open surgical technique for interlocking nailing is superior.

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RESEARCH ARTICLE

FIBROMYALGIA IN HEPATITIS C PATIENTS; A CROSS-SECTIONAL STUDY FROM PAKISTAN

Sadia Asif [1], Muhammad Shahbaz Ashraf [2], Nazia Mumtaz [3], Muhammad Umair Abid [1]
Neelum Zaka [4], Lubna Meraj [5]

[1] Senior Registrar, Shalamar Hospital Lahore, Pakistan
[2] Senior Registrar, Benazir Bhutto Hospital, Rawalpindi, Pakistan
[3] WMO, THQ Hospital, Kallar Syedan, Rawalpindi, Pakistan
[4] Assistant Professor, Shifa Tameer-e-Millat University, Islamabad, Pakistan
[5] Associate Professor, HoD MU-I, Benazir Bhutto Hospital, Rawalpindi, Pakistan

ABSTRACT

Fibromyalgia syndrome (FS) is a chronic musculoskeletal illness involving anatomic locations of tender points and discomfort at certain levels. The study was carried out to ascertain the prevalence of hepatitis C virus Infection in Fibromyalgia Patients.

Methodology: *This cross-sectional descriptive study was conducted at the Mayo Hospital Lahore from 1st January to 30th May 2019. The patients who presented to Mayo Hospital Lahore with hepatitis C virus infection throughout the research period were included by consecutive sampling. Using the widespread pain index and severity scale score resulting from hepatitis C infection, patients were evaluated for the existence of fibromyalgia, and information was entered on a predesigned questionnaire. Using SPSS version 24.0, the data that was recorded on the questionnaire was analyzed. The Chi-square test was applied with a significant p-*value *< 0.05.*

Results: *The prevalence of fibromyalgia was reported to be 46.4% (26 individuals), while 53.6% (30 patients) did not have the condition. Fibromyalgia was present in 33.3% of patients below the age of 30 years, 47.1% of patients between the range of 31yrs -50yrs, and 50% of patients above the age of 50 years (p=0.774). In terms of gender, there were 66.7% of female patients with fibromyalgia as opposed to 17.4% of male patients (p=0.001). In terms of WPI, the mean of male respondents was 5.52±5.60, while that of female respondents was 5.52±5.62. (p=0.05) The difference was statistically significant. In contrast, the severity scale score for male respondents was 4.26±3.32 and for female respondents it was 7.12±3.14. The difference was statistically significant (p-value = 0.002).*

Conclusions: *Hepatitis C infection increased the risk of fibromyalgia. Fibromyalgia is highly correlated with gender.*

Keywords: *Fibromyalgia, Hepatitis C Infection, Severity Scale Score (SS), Wide spread Pain Index (WPI)*

INTRODUCTION

A chronic musculoskeletal illness called fibromyalgia syndrome (FS), which is described as widespread tender points and discomfort at certain anatomic locations. Primarily it affects middle-aged women. The prevalence varies depending on the demographic. For adult women, it ranges between 0.7% and 13%, while for adult men, it ranges between 0.2% and 3.9% [1]. A long-standing disorder known as fibromyalgia a new name of old condition, which is described by persistent widespread tender points, exhaustion, disturbed sleep and cognitive impairment[1]. Interstitial cystitis (painful bladder syndrome), headache, temporomandibular joint disorders, irritable bowel syndrome, mastalgia and dysmenorrhea are a few somatic and functional diseases that are frequently linked to biopsychosocial model. Psychological symptoms common in fibromyalgia patients include anxiety and sadness. The majority of patients arrive with a combination of physical, psychological and cognitive symptoms[2]. It is usually related with somatic and functional illnesses for example interstitial cystitis (painful bladder syndrome), headache, temporomandibular joint disorders, irritable bowel syndrome, mastalgia and dysmenorrhea. Anxiety

Correspondence:
Dr. Lubna Meraj
Associate Professor, HoD MU-I
Benazir Bhutto Hospital, Rawalpindi, Pakistan
Email: Lubnamerajch@gmail.com

and melancholy are two psychological symptoms that fibromyalgia sufferers frequently experience. Most patients enter with a mix of cognitive, psychological and somatic problems[3]. Infection such as Epstein-Barr virus, parvovirus, Borrelia (Lyme disease) and campylobacter infection has been proven to be temporally connected to fibromyalgia among other viral and bacterial infections[4,5]. Patients with hepatitis C or HIV infection had fairly increased rates of fibromyalgia[5,6]. Patients with HCV infection may commonly display rheumatological symptoms such arthralgia, myalgia, arthritis, myositis and fibromyalgia. Other rheumatological symptoms include essential mixed cryoglobulinemia, vasculitis, and sicca symptoms[7,8]. Although, the precise causes of these extra hepatic symptoms of HCV infection and the rheumatological manifestations are yet unknown and it has been hypothesized that immunological processes may be involved. Autoantibodies are frequently seen in the circulation in patients with persistent viral hepatitis. In addition to the deposition of circulating immune complexes in the tissues, viral antigens or viruses can cause local immune complex development that interacts directly with extra hepatic tissues[9]. According to current research, bacterial or viral infections influence the way that pain is processed through neuronal as well as non-neuronal mechanisms by activating certain receptors and releasing pro-inflammatory cytokines[10]. In response to viral and bacterial illness, the peripheral (PNS) as well as central nervous systems (CNS) experience neuroinflammation[10]. Bacterial infection may control primary sensory neurons directly or indirectly by activating receptors on neurons and glial cells.[10] Activation of glial mediators and non-neuronal cells like macrophages or Schwann cells in the PNS. Patients with fibromyalgia have shown signs of both neuro-inflammation and systemic inflammation[11, 12].

For the majority of the 20th century, fibrositis or widespread fibrositis was employed as the diagnostic term[13]. Since the American College of Rheumatology (ACR_1990) categorization criteria were published, fibromyalgia has gained widespread acceptance as a diagnosis and is often utilized by doctors and researchers. It was founded on the opinions of several rheumatologists in the ACR who specialize in fibromyalgia. The primary symptom is widespread chronic tender points that have persisted for more than three months, and the crucial symptoms are 11 of 18 sensitive spots that may be felt while applying pressure of around 4 kg to the axial bone and muscle tendons. The tender point examination is not included in the ACR 2010 diagnostic criteria. Wide Pain Index (WPI) and symptom severity(SS) are used to score patient reports of symptoms(SS). WPI score and the amount of uncomfortable body parts are correlated (total score 0-19). The intensity of the four categories of symptoms—fatigue, restless sleep, cognitive impairment, and somatic symptoms—ranges from no symptom to severe symptoms (0–3). SS scale total scores range from 0 to 12. The Wide Pain Index (WPI 7) and severe symptoms (SS 5) or Wide Pain Index (WPI 3) and (SS 9) criteria define fibromyalgia. Therefore, fibromyalgia and chronic widespread tender points/ pain might be seen as two different chronic syndromes, with fibromyalgia serving as a diagnosis for those who also have concurrent physical and psychological symptoms.

METHODOLOGY

At the Mayo Hospital in Lahore, the hepatitis C patients were enrolled for the diagnosis of fibromyalgia within the designated time period (1st January, 2019 to 30th May 2019, and their age, gender, and known risk factors were taken into account). Hypothyroidism, vitamin D deficiency, steroid intake, hepatitis B, HIV, DM and anemia were excluded by biopsychosocial model (history taking, clinical examination) as well as biochemical testing. The questionnaire data was reviewed and analyzed by using SPSS version 24.0. The frequency data with percentage as well as Means±SD were determined for categorical variables. Chi-square test was performed to examine the relations between various components and socio-demographic data or biopsychosocial model. Wide pain index (WPI) and symptom severity (SS) among gender and duration were calculated using an independent t-test (years). P-values under 0.05 were measured statistically significant.

RESULTS

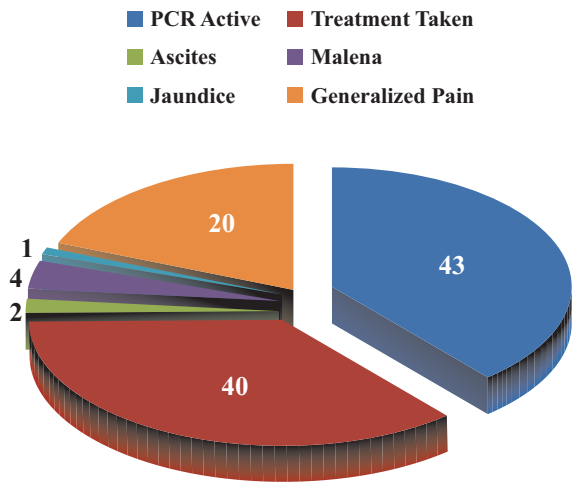
Total 56 patients with hepatitis C presented during the specified time period. Fibromyalgia was reported to be present in 46.4% (26 patients) and 53.6% (30 patients) were not suffering from fibromyalgia. Out of 56 patients presented, 58.9% of patients (33) were males and 41.1% (23) were females, thus making male to female ratio as 1.0:1.435 respectively. The mean WPI was 7.29±5.76 and Severity symptoms showed that 5.95±3.49. Table-I shows the gender and respective age group distribution with mean age as 45.43±11.15 years among the patients with hepatitis C infection. Regarding known factors, there were 10.7% (06) patients having diabetes mellitus (DM), hypertension was seen in 7.1% (04) patients while known symptoms for 3 months were 51.8% (29).

Table I: Frequency distribution of characteristics and certain factors among patients

Variables		Frequency	Percentage
Fibromyalgia	Yes	26	46.4
	No	30	53.6
Age (Years) 45.43±11.15*	≤ 30	06	10.7
	31-50	34	60.7
	> 50	16	28.6
Gender	Males	33	58.9
	Females	23	41.1
Diabetes Mellitus	Yes	06	10.7
	No	50	89.3
Hypertension	Yes	04	7.1
	No	52	92.9
Symptoms for 3 months	Yes	29	51.8
	No	27	48.2
Total		56	100

*Mean ± SD

Figure I: Various factors among Hepatitis C patients.



There were 33.3% patients with fibromyalgia that were having age ≤ 30 years, 47.1% were of ages 31 to 50 years, and 50% were > 50 years (p-value = 0.774). Regarding gender, there were 17.4% male patients with fibromyalgia as compared to 66.7% female patients suffering from the disease (p-value = <0.001) as shown in table no: II.

Table II: Age and Gender association with Fibromyalgia among hepatitis C patients

Variable		Fibromyalgia		p-Value
		Yes (%)	No (%)	
Age (Years)	≤ 30	02 (33.3%)	04 (66.7%)	0.774
	31-50	16 (47.1%)	18 (52.9%)	
	> 50	08 (50%)	08 (50%)	
Gender	Males	04 (17.4%)	19 (82.6%)	<0.001*
	Females	22 (66.7%)	11 (33.3%)	
Total		26 (46.4%)	30 (53.6%)	

* Significant (p-value ≤ 0.05)

The mean shown by male respondents was 5.52±5.60 regarding WPI and among females it was 8.52±5.62. The difference was statistically significant (p-value = 0.05). Whereas severity scale scores showed that male respondents had 4.26±3.32 and female respondents showed mean 7.12±3.14. The difference was statistically significant (p-value = 0.002). Comparing the two scales with disease duration of 3 or more than 3 years show wide spread pain index 7.61±5.42 and 6.61±6.52 respectively. The difference was statistically insignificant (p-value = 0.256). Comparative severity scale score showed mean of 5.58±3.61 and 6.72±3.18. The difference was statistically insignificant (p-value = 0.551) as shown in table no: 3.

Table 3: Wide spread pain index and Severity Scale Score regarding gender and Disease Duration (Years)

Scales	Gender	Mean ± SD	p-value
Wide Spread Pain Index	Males	5.52±5.60	0.05*
	Females	8.52±5.62	
Severity Scale Score	Males	4.26±3.32	0.002*
	Females	7.12±3.14	
Scales	**Disease Duration**	**Mean ± SD**	**p-value**
Wide Spread Pain Index	≤ 3	7.61±5.42	0.256
	> 3	6.61±6.52	
Severity Scale Score	≤ 3	5.58±3.61	0.551
	> 3	6.72±3.18	

* Significant (p-value ≤ 0.05)

DISCUSSION

Hepatitis C virus infection is a rising and significant healthcare problem in Pakistan. The various grades of HCV are observed including the acute and chronic infections leading to liver damage, cirrhosis, and hepatocellular carcinoma. In Hepatitis C patients' fibromyalgia is a problem that requires prompt attention. In our study, individuals with hepatitis C had a 46.4% fibromyalgia prevalence rate. Within HCV clinic groups, the rates of prevalence ranged from 50 to 81 percent for musculoskeletal pain[14,15]. Patients with chronic Hepatitis C Virus frequently experience arthralgias; estimates range from 9 to 23%.

According to all available research, the prevalence of Fibromyalgia in people with Hepatitis C Virus ranges from 10.0 to 18.9%[16]. These prevalence rates are greater than those of Fibromyalgia in cirrhotic patients and healthy individuals. Even though these studies suggest a link between Fibromyalgia and chronic Hepatitis C Virus, at least one recent study questions this relationship. As a result of this study's prospective comparison of the prevalence of HCV infection in Fibromyalgia patients with that of Hepatitis C Virus in the general population, it is possible that chance rather than pathophysiology may be to responsible for the association between Hepatitis C Virus and Fibromyalgia. However, one research stood out as a clear exception. Only 46% of Fibromyalgia FM-positive cases in a tertiary pain clinic reported extensive pain, according to Wolfe et al. This posed numerous significant difficulties[4]. According to their findings, 10.4% of Fibromyalgia patients experienced unilateral pain syndromes, 9.6% only experienced pain in the upper body or in the head and trunk, and 10.4% experienced local pain syndromes that only affected one or two quadrants of the body. The remaining samples displayed further types of "incomplete" distribution patterns[12]. Two pathogenetic explanations for how HCV infection could cause FM have been put out to far. According to the first, viral infection and subsequent HCV-induced inflammation may set off a series of biochemical processes that result in FM development [18]. However, it is unclear, given the information to date, whether FM, an extra hepatic manifestation, is caused by immunological processes or hepatic injury. For instance, several investigations have shown that individuals with severe HCV liver disease had a higher incidence rate of Fibromyalgia[17]. Other research has shown no connection between the symptoms of Fibromyalgia and the degree of liver disease, the source of infection, or the status of therapy[18]. Furthermore, it has been demonstrated that co-diagnosis of Fibromyalgia and Hepatitis C Virus can happen in the absence of consistent changes in liver enzymes[19]. Several studies have informed the percentage of participants meeting the 2011 (or 2010) criteria by the low wide pain index WPI category, including 4.4% of 1411 FM patients in a German clinical research[17], 15.5% of 71 participants in a clinical research conducted in Korea [18]. 2.7% of 80 patients in a Spanish population [20], 17% of 52 cases in a German population study [16], 6-7% of 514 patients in the study of the ACR 2010 criteria [17], 62% in the present report, and 25.9% in a 27-subject Scottish population survey[21]. It should be highlighted that the broad pain estimate used in the German population survey included chest, head, and stomach pain into account.

The prevalence of HCV in Pakistan was estimated to be 12.55% in 2017 by Arshad et al [22]. However, a review conducted by Umar et al from 1992-2208 showed 4.7% prevalence, varying from 0.4% to 33.7% in different regions. It was concluded that Pakistan has higher prevalence than neighboring countries. Also, the variation in prevalence could be due to pocket of infections in various parts of the country [23]. Despite of the significant burden of HCV, we found limited data from Pakistan addressing the Fibromyalgia in HCV cases. Hence, this study may provide the local data that can be compared to international figures. This may help to identify and address the fibromyalgia for better quality of life in HCV cases. Authors suggest further regional studies to address the various aspects of Fibromyalgia.

CONCLUSION

Fibromyalgia occurrence due to hepatitis C infection was higher. Gender was found significantly associated with fibromyalgia. Females had higher percentage suffering from fibromyalgia than males. The wide spread pain index and severity symptom scale score was also significant regarding gender.

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RESEARCH ARTICLE

INCIDENCE OF INDUCED ASTIGMATISM AFTER PHACOEMULSIFICATION CATARACT SURGERY AT HITEC IMS

Shahzad Waseem, Dilshad Alam, Haroon Javaid, Rabia Ashraf, Nargis Zahara, Najeeba Hareem

Department of Ophthalmology, HITEC Institute of Medical Sciences, Taxila, Pakistan

ABSTRACT

Objective:

The Purpose of this study was to measure the induction of astigmatism after phacoemulsification.

Setting: *This study was done at HITEC-IMS Taxila, Pakistan for 5 months (Dec 2021 to April 2022).*

Method: *It is a prospective interventional study*

Results: *The occurrence of post operative astigmatism is minimum when patients were examined one month post operatively.*

Keywords:

Best Corrected Visual Acuity (BCVA), Cataract, Surgery Induced Astigmatism SIA, Keratometry readings, Phacoemulsification, Uncorrected Visual Acuity (UCVA)

INTRODUCTION

Cataract is one of the common causes of blindness and a decrease in vision. WHO is trying to alleviate this irreversible cause of blindness. ((WHO Vision 2020). 2013)[1]. The position, type, and other factors like corneal incision may cause surgery-induced astigmatism after cataract surgery. Temporal clean corneal incisions have been reported to generate only minor alterations to the corneal cylinder[2]. Donders was the first one to demonstrate that a change in corneal curvature is an unwanted outcome after cataract surgery. There have been various studies on corneal astigmatism and intracapsular cataract surgery. At the turn of the century, earlier surgical techniques began without sutures. Both these and later procedures, which used one or two massive gut sutures, resulted in an out-of-control prevalence of astigmatism[3]. Intra-Ocular Lens (IOL) power and medically induced astigmatism are the two main determinants of the refractive condition of the eye after phacoemulsification and intraocular lens implantation (PE+IOL) (SIA)[4].

Correspondence:
Dr. Shahzad Waseem
Department of Ophthalmology
HITEC Institute of Medical Sciences, Taxila, Pakistan
Email: 2drshahzadwaseem@gmail.com

The surgeons intended to reduce postoperative refractive errors in order to meet rising patient demands. SIA remains a challenge in the postoperative period because the primary goal is to deliver successful visual rehabilitation. It is commonly recognised that only patients with 0.50 diopters (D) of astigmatism do not require spectacles for distance activities, and that the necessity for spectacles increases dramatically with each diopter of astigmatism[5]. Temporal clean corneal incisions have been reported to generate only minor alterations to the corneal cylinder. SIA following clean corneal incisions of sizes ranging from 3.2 mm to 5.2 mm has also been compared in several studies[6].

Modern cataract surgery aims for quick vision recovery and the best possible Uncorrected Visual Acuity (UCVA) with little post-operative astigmatism. Modern cataract surgery techniques allow for quick visual recovery, but Surgically Induced Astigmatism(SIA) is still a typical stumbling block to perfect vision[7].

OBJECTIVES:

The objective of the study was to measure the astigmatism being induced by phacoemulsification, one-month post operatively.

MATERIALS AND METHODS:

The study was conducted in a hospital setting. The study

design was prospective, interventional study.

The study was conducted at HITEC-IMS, Taxila during the time period of 5 months, from December 2021 to April 2022. A sample size of 80 patients who had cataracts, age between 40 to 75 years, were included in the study. The phaco technique was used for cataract surgery during the study time. The study was performed by the same surgeon to lessen the human error. A thorough anterior and posterior segment examination was conducted to rule out any co-morbidity.

Astigmatism was measured by keratometery before and one month after the surgery, and the results were compared.

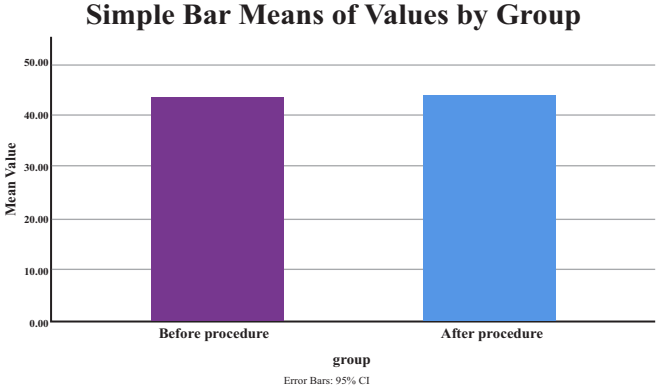
Statistical analysis:

SPSS 28 was used to do the statistical analysis. Paired sample t-test was applied to compare the results of means of pre-operative k readings and post-operative k readings. *p*-value <0.05 was statistically significant.

RESULTS:

A total of 80 patients were included in this study. Pre-means k reading value and post-means k reading value were calculated. The pre means K-reading value was (43.51 ± 1.62) and the post means k reading value was (43.75 ± 1.87). The *p*-value was found to be .072. *p*-value is insignificant after comparing both pre-operative and post-operative means.

Figure: 1



DISCUSSION:

This study was done at HITEC Hospital Taxila, the surgeon operated on 80 patients the incidence of post-operative astigmatism was minimum. This demonstrates that phacoemulsification causes only minor astigmatism. Our findings are supported by a number of other studies.

According to a study, a 2.8-mm corneal incision in phacoemulsification caused a relatively little corneal refractive shift on average, but there were variances depending on where the incision was made[8]. In light of prior studies, the corneal incision size has gradually reduced, and past studies have shown that a small incision size is associated with a fast recovery and less astigmatism. Although the size, location, and shape of the incision all affect the astigmatic axis shift, it has been shown that the incision size significant impact on SIA[9]. Modification of incision location such as incision in the steepest meridian of pre existing astigmatism highly reduces the chances of SIA[10]. Reduction of SIA also depends on the approach of surgical incision such as temporal incisions induce less SIA when compared to superior corneal or nasal incisions[11]. When observed over a longer length of time, it was discovered that a superotemporal (10-11 O'clock) 3.2 mm incision hardly generates any astigmatism or induces any substantial change in the existing preoperative astigmatism, i.e. less than 0.50 diopters in general[12]. One study utilised analysis of variance (ANOVA) to compare SIA in the right and left eyes, as well as between surgeons. There was no significant difference in SIA between surgeons in the first and sixth postoperative months ($p > 0.05$). Furthermore, SIA showed a statistically significant decrease from the first to the sixth month ($p = 0.003$)[13]. At 12 weeks after surgery, the mean SIA in the 3.5 mm incision group was 0.58 and 0.28 D, the SIA achieved in our study in the 3.5 mm incision group was lower than that reported by Barequet et al[13] and Khokhar et al[14]. Sheoran K et al., also reported that phacoemulsification cataract surgery also leads to compelling improvement in UCVA and BCVA after comparing pre and post-operative reading evaluations[15]. Almost all the studies in this area have shown that there is less incidence of astigmatism after phacoemulsification, so phacoemulsification is the best technique to remove cataract.

CONCLUSION:

On the basis of our study, we have found that phacoemulsification is the best method for managing cataract. It is suggested that where possible, this procedure should be adopted for cataract surgery and more eye specialists should be trained to learn this procedure.

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REVIEW ARTICLE

ROLE OF NLRP3 INFLAMMASOMES IN PATHOGENESIS OF TYPE 2 DIABETES MELLITUS-AN OVERVIEW

Aneela Shabbir, Maryam Wahid, Hajira Siddique

Department of Biochemistry, Foundation University Medical College, Islamabad Pakistan

ABSTRACT

Diabetes mellitus type 2 (T2D) is a multifactorial metabolic disorder associated with chronic inflammation. Several mechanisms have been postulated for its pathogenesis. One recently postulated mechanism is based on the activation and assembly of inflammasomes. Intracellular sensors recognize damage associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). This leads to assembly and activation of inflammasomes starting a cascade of events resulting in chronic inflammation in T2D. These inflammasomes are under extensive study to understand the signaling pathways involved in the pro-inflammatory environments among patients of T2D. NLRP3 (Nucleotide binding oligomerization domain, LRRs and pyrins) mediated secretion of cytokines plays a vital role in the pathogenesis of T2D and associated complications. A better understanding of this inflammasome can lead to discovering novel therapies for T2D treatment. Moreover, NLRP3 inhibitors can be used to slow down the progression of disease and to prevent complications in T2D.

Keywords: *Diabetes Mellitus, Damage associated molecular patterns, Pathogen associated molecular patterns, Pyroptosis, NLRP genes*

BACKGROUND

T2D is a major health issue with global impact. It results from interplay of multiple risk factors. Positive family history and environmental factors increase the chances of developing T2D. Chronic inflammatory response remains the backbone of the pathogenesis. Circulating levels of various inflammatory mediators such as interleukins, tumor necrosis factors and adipokines is high especially in obese patients.[1] Adipose tissue is not merely a collection of adipocytes but is an active secretory tissue releasing pro-inflammatory cytokines and suppressing anti-inflammatory mechanisms. IL-1β is particularly known for impairment of β-cell function and insulin resistance.[2] Expression of inflammatory cytokines is also increased in T2D and plays important role in development of associated microvascular and macrovascular complications. Various exogenous and endogenous factors induce immune response via intracellular receptors which are part of inflammasomes and a series of events ultimately leads to pyroptosis.

Correspondence:
Dr. Aneela Shabbir
Department of Biochemistry
Foundation University Medical College, Islamabad
Email: aneela.shabbir@fui.edu.pk

Inflammasomes

Inflammasomes were first described by Tschopp and colleagues in 2002 and the knowledge pool has expanded till date substantially.[3] Inflammasomes are complexes of high molecular weight molecules present in cytosol of immune cells. Pattern recognition receptors (PRR) trigger assembly of inflammasomes in response to stimulus by PAMPS or DAMPS.[4] Five receptors have been identified till now and include nucleotide binding oligomerization domain (NOD), leucine rich repeat (LRR) containing NLR family members namely NLRP1, NLRP3 & NLRC4, pyrin and proteins absent in melanoma 2 (AIM2).[5] The activation mechanism and pathways of these are very well characterized. There are certain other less understood pathways stimulated via NLRP6, NLRP7, NLRP12, interferon inducible protein 16 and retinoic acid inducible gene etc. Ligand binding with these receptors results in activation and oligomerization of sensor followed by recruitment of adapter protein. NLRP3 activation/oligomerization requires a NIMA(Never in Mitosis geneA) related kinase 7 (NEK7) which gets attached to LRRs of NLRP3. Activated receptors recruit ASC adapter protein. It consists of PYD(Pyrin domain) & CARD(Caspase recruitment domain). PYD & CARD

are mandatory for recruitment of pro caspase-1 which ultimately leads to cleavage of precursor cytokines to mature cytokines initiating pyroptosis.[6]

NLRP family

Various NLRPs (Nucleotide binding oligomerization domain, LRRs and pyrins) have been identified which play role in inflammation and apoptosis. These proteins, also referred as NALP belong to NOD like receptors and are products of genes located on two chromosomes. Chromosome 11p15 contains genes for NLRP6, NLRP10 & NLRP14. NLRP1 & NLRP3 genes are present on 17p13.2 and 1q44 respectively. Rest of the NLRP genes are located on chromosome 19q13.4.[7]

Expression of NLRP genes varies across tissues. All the NLRP receptors are expressed in white blood cells. NLRP1 expression is high in nerve cells especially in pyramidal cells and oligodendrocytes. Multiple alleles of NLRP1 have been identified across various populations making it highly polymorphic gene. NLRP1, NLRP10 and NLRP3 are highly expressed in keratinocytes of epidermis. NLRP6 is mainly expressed in enterocytes where it plays role in fight against viral infections.[8]

NLRPs and inflammation:

NLRP1 is considered a key inflammasome sensor in keratinocytes which gets activated by UV radiation and is believed to play role in sunburns.[9] Mutations resulting in gain of function of NLRP1 are risk factor for developing skin cancers. It is also associated with auto-inflammation resulting in arthritis[10] and dyskeratosis[11]. Recently role of NLRP1 in pathogenesis of diabetes mellitus has been studied. It was established that NLRP1 polymorphism is associated with gasdermins (GSDMs) mediated pyroptosis in cases of T1D.[12]

NLRP3 inflammasome is under extensive study for its role in development of chronic inflammation in T2D. The caspase-1 activation results in maturation of pro-inflammatory cytokines which play important role in pathogenesis of T2D as well as development of complications.[13]

NLRP3 and its role in T2D

NLRP3 inflammasomes are activated by obesity induced danger signals in T2D patients. Studies on mice revealed palmitate-induced activation of NLRP3 leading to impaired insulin signaling and decreased glucose tolerance. Levels of chemokine 10, CCL2 and interferon-γ were reduced in NLRP3 knockout mice.[14]

Evidence suggested that level of NLRP3, IL-1β, IL-18 and ASC mRNA is elevated in patients of T2D. Studies also showed that hyperglycemia induces the expression of toll like receptors (TLR) especially TLR2 and TLR4. Raised levels of other molecules capable of activating TLR including NLRP3 are present in cases of T2D. These are high mobility group box-1 (HMGB1- high mobility group box-1) and endotoxins.[15] Hyperglycemia and oxidized LDL-cholesterol initiate priming of islet amyloid polypeptide (IAPP) in T2D, activation of NLRP3 inflammasome mediated generation of mature IL-1β.[16]

Several studies have established that expression of NLRP3 is increased inpatients of T2D. Ruscitti et al reported increased expression of NLRP3 in monocytes of T2D patients and raised levels of resultant inflammatory cytokines.[17] Similar results were later on reported by other researchers. The risk factors of T2D may also upregulate NLRP expression, thus participating in pathogenesis and development of complications. Free radicals especially reactive oxygen species (ROS) are strong activators of this inflammasome.[18] Another molecule, Thioredoxin interacting protein damages β-cells via upregulation of NLRP3.[19] Therefore, NLRP3 inflammasome seems to be a key player in pro-inflammatory environment seen in T2D patients.

NLRP3 depletion is linked with declined inflammation inT2D

Several studies were conducted in which NLRP3 or related molecules knockout animals were used to learn about their association with inflammation in T2D. Yun Hee et al established in their study that ASC & NLRP3 knockout mice have higher insulin levels compared to control group with similar conditions.[20] Other studies have revealed that IL-1β expression in adipocytes is also decreased by eliminating NLRP3.[21] Penjovic et al demonstrated that transfection of macrophages in Galectin-3(-/-) mice, administered with siRNA targeting NLRP3 resulted in altered IL-1β production.[22] All these studies reflect the strong relation between NLRP3 inflammasome activation and inflammation in T2D patients.

NLRP3 Polymorphism and T2D

Several studies investigated the association of NLRP3 polymorphism and T2D progression. It was reported that polymorphism and mutations resulting in gain in function of NLRP3 contribute to pathogenesis of T2D

and increased risk of complications. NLRP3 rs35829419 was found to be linked with vascular complications especially myocardial infarction.[23] In another study, it was reported that rs4925659 GG, rs10925027 CC, rs10754558 GG and GC+GG genotypes are at high risk of chronic inflammation and T2D.[24] A study on Indian population revealed significant association between NLRP3 GG genotype at rs10754558.[25]

Pharmacological interventions targeting NLRP3

Since the role of NLRP3 inflammasome has been established, several dietary as well as pharmacological interventions to inhibit NLRP3 have been studied. The researchers studied effects of these inhibitors on glycemic control and development of complications. The role of dietary unsaturated fatty acids in slowing down the progression of complications is established. A study by L'homme and colleagues demonstrated the key role of unsaturated fatty acids in NLRP3 inhibition among humans.[26] Similarly polyunsaturated fatty acids and omega-3 fatty acids exert their beneficial effects via NLRP3 suppression. PSPC (purple sweet potato color) derived flavonoids also inhibit NLRP3 functioning. This is associated with reduced risk of atherosclerosis in patients of T2D. Lamkanfi et al reported in their study that glyburide exerts its action by inhibition of IAPP mediated activation of NLRP3.[27] Later on Luo and colleagues established that rosuvastatin down-regulates NLRP3 expression, thus reducing inflammation in T2D patients with cardiomyopathy.[28] Various other inhibitors of NLRP3 have been investigated to treat diseases related with this inflammasome activation. These include p58, Erratum, acrylamide derivatives and tripartite motif protein 30 and promising results were reported in multiple studies.

CONCLUSION

The key role of inflammasomes in initiation and progression of inflammatory disorders is established. As T2D pathogenesis and development of complications especially vascular complications is also the result of chronic inflammation, the role of inflammasomes in DM is extensively studied. NLRP3 inflammasome activation and gain of function was found to be associated with T2D, so it was hypothesized that inhibitors of NLRP3 may be the next therapeutic option for T2D. Various inhibitors were tried in vivo and in animal studies and were found to be useful. Micro RNA based inhibition of NLRP3 was also studied. Further research in this domain may be helpful in devising new weapons for fight against T2D. The molecular knowledge of NLRP3 gene and inflammasome can be translated to design new diagnostic tools and therapeutic measures for prevention and treatment of T2D.

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CASE REPORT

LAPAROSCOPIC CHOLESYSTECTOMY IN A RARE CASE OF SITUS INVERSUS TOTALIS

Muhammad Imran[1], Aurangzeb Khan[2], Ume Sughra[3], Shimron Innocent Bhatti[4], Muhammad Taimur[5]

[1] Associate Professor of Surgery, Fauji Foundation Hospital Rawalpindi, Pakistan
[2] Professor of Surgery, Fauji Foundation Hospital Rawalpindi, Pakistan
[3] Professor & Director Research, Al-Shifa School of Public Health, Al-Shifa Trust Eye Hospital Rawalpindi, Pakistan
[4] Postgraduate trainee Surgery, Fauji Foundation Hospital Rawalpindi, Pakistan
[5] Assistant Professor of Surgery, Fauji Foundation Hospital Rawalpindi, Pakistan

ABSTRACT

Situs inversus is a rare congenital anomaly with an abnormally positioned gall bladder to the left side. Normally these patients live up to their normal life expectancy but in a few with cardiac abnormalities, it might be reduced. The formation of gallstones in these patients is a fairly common condition. The condition may be asymtomatic but can often produce epigastric or left hypochondrial pain associated with nausea. The following report is a rare case of left-sided gallbladder with mirror image anatomy of abdominal visceras. Mostly these patients are managed with open cholecystectomies but we performed Laparoscopic Cholecystectomy in this case.

INTRODUCTION

Situs inversus, or its most common form, situs inversus totalis, is a rare condition that occurs in 1 out of 10,000 people, whereby the abdominal organs are laterally rotated in comparison to their normal counterpart locations.[1] It is often associated with dextrocardia, a condition in which the heart too is located on the right side, as opposed to the left. The condition in itself does not increase likelihood of any disease due to the relation of the organs to each other being unchanged and most people may thus live without ever knowing of it, unless it is incidentally diagnosed.[2]

Cholelithiasis is a fairly common condition wherein the person will have formation of stones in their gall bladder. These stones may vary in composition, such as cholesterol stones or bile salt stones, and are often accompanied by the presence of inflammation. The condition may be asymptomatic, but can often produce pain, both local and referred, with jaundice being present in case of bile passage blockage, and may lead to further complications such choledocolithiasis and pancreatitis.[3] It is diagnosed through radiological techniques such as ultrasonography after ascertaining the symptomatology.

Correspondence:
Dr. Muhammad Imran
Department of Surgery
Fauji Foundation Hospital Rawalpindi, Pakistan
Email: imran.muhammadimran@yahoo.com

CASE REPORT

54 years old lady with no known co-morbids presented to the outpatient department with a 6 months history of intermittent left hypochondrial pain. Her pain radiated to the left shoulder blade, and was associated with malaise and nausea.

Ultrasound abdomen showed left sided gall bladder with multiple small stones. Abdominal ultrasound also demonstrated the mirror image anatomy of other abdominal visceras. Dextrocardia was present on her chest X-ray. After cardiac and respiratory evaluation her laparoscopic cholecystectomy was planned.

The setting in operation theatre was modified with surgeon and camera assistant standing on right side, second assistant on left side and monitor placed towards the left shoulder. Total four ports were inserted in modified position, infra-umblical, epigastric and two left lateral. Left sided gall bladder and liver were identified on laparoscopy. Calot's triangle dissection was started near the gall bladder and identified the normal mirror image anatomical relationship of cystic duct and cystic artery with common bile duct. No associated anomaly was found. Cyst duct and artery were clipped and divided, gall bladder dissected out and extracted through epigastric port. Patient had uneventful recovery and discharged on first postoperative day. Follow up was unremarkable.

DISCUSSION

Situs inversus is a rare condition which occurs due to malrotation of abdominal organs during fetal life. It is commonly associated with dextrocardia. These patients have no raised chances for any abdominal disease, nor are they any more predisposed to cardiac diseases more than their normal counterparts. However they are predisposed to Kartagener's syndrome.[4]

This condition can be complete, thereby known as situs inversus totalis; partial; or there may be isolated mirroring of the location of an abdominal organ, known as situs ambiguus.[5] Patients who have levocardia along with situsinversus however, are at increased chances of anatomical diseases such as transposition of the great vessels, as are those with isolated dextrocardia.

There is no evidence showing that the prevalence of cholelithiasis is any different in people with situsinversus than in those without, and in rare cases, there could an isolated left sided gall bladder present, which too would present with symptoms mimicking the aforementioned case. As such the biggest difficulty present in the management of this case is correct diagnosis, as physical examination as well as radiology may incur confusion in the management.[6,7] When performing surgery, it is of paramount importance for all the medical personnel involved to be informed of the anomaly. It is also advisable that these patients keep some form of condition identification, such as a card or wrist band, so that future consultations may go more smoothly.

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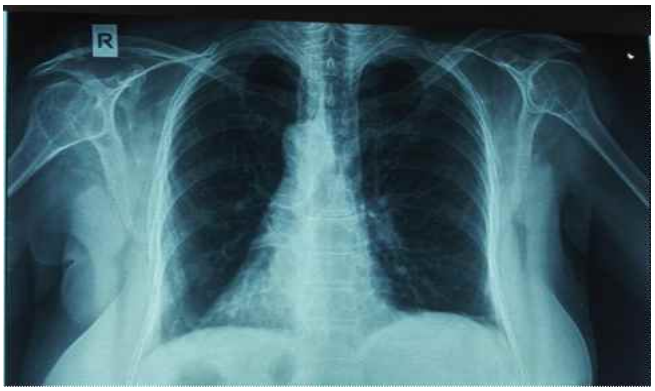

Figure: 01 Dextrocardia shown on Chest X-ray

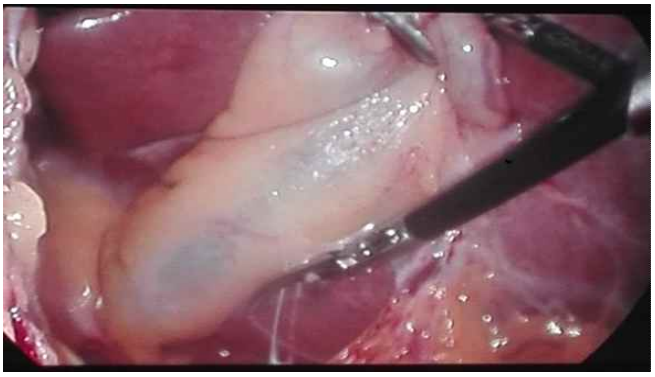

Figure: 02 Calot's triangle

Figure: 03 Laparoscopic port positions and anterior abdominal wound showing mirror image of the routine laparoscopic cholecystectomy

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