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EDITORIAL

New and Emerging Therapeutic Agents for the Management of SARS-Cov-2 Coronavirus Infection COVID-19

Sayed Subhan Bukhari, Shaun H Livsey

COVID-19 emerged as a new severe acute respiratory illness in Wuhan, China in December 2019 and rapidly spread worldwide to become a global pandemic.[1] Although the figures keep changing on daily basis, by the end of October 2020, over 44 million people have been diagnosed with COVID-19 worldwide, according to World Health Organization. The pandemic has claimed more than a million human lives so far and resurgence in the number of new cases and continued growth in some countries has threatened both high and low-resource countries alike.

In January 2020, the virus responsible for the Coronavirus Infectious Disease 2019 (abbreviated as COVID19) was isolated and its RNA genome sequenced and shared globally online.[2,3] From complete genome sequencing it transpired that the cause of the severe acute respiratory illness that became known as COVID-19 is in fact a novel coronavirus, named SARS-CoV-2. Since then every so often new information about the virus and the new infection is emerging and history is constantly being rewritten. Subsequent phylogenetic analysis of the viral genome sequence suggests that SARS-CoV-2 originated in animals, probably bats, and was transmitted to other animals before crossing the human species barrier at the Huanan wet market in Wuhan City.[4,5,6]

The search for specific therapeutic drugs to effectively treat COVID-19 commenced as early as the discovery of the virus itself. However, with many studies carried out independently in small numbers of patients, there is a risk that such trials may lack sufficient statistical power for clinical recommendations. In this editorial, we will describe selected agents which are under investigation in large scale studies and which are more likely to produce robust outcome data for the efficacy and safety of these agents in the management of COVID-19. These studies include the World Health Organisation (WHO) SOLIDARITY study and the French Discovery study.[7,8]

WHO Study, "SOLIDARITY"

This is an international clinical trial to help find out an effective treatment for COVID-19 which was launched by the World Health Organization (WHO) and partners. It is one of the largest international randomised trials for COVID-19 treatments, enrolling almost 12, 000 patients in 500 hospital sites in over 30 countries. This study is evaluating the effect of drugs on 3 important outcomes in COVID-19 patients: mortality, need for assisted ventilation and duration of hospital stay.[7,8]

The study compares treatment options against standard of care to assess their relative effectiveness against COVID-19. By enrolling patients in multiple countries, the Solidarity Trial aims to evaluate whether any of the drugs improve survival or reduce the need for ventilation or reduce the duration of hospital stay. The trial is open to adding other drugs based on emerging new evidence. However, until such time as there is sufficient evidence, WHO cautions physicians and medical associations against recommending or administering unproven treatments to patients with COVID-19 or people self-medicating with such agents. WHO guidance on compassionate use can be found on the following link: https://www.who.int/news-room/commentaries/detail/off-label-use-of-medicines-for-covid-19.

The Solidarity Trial published interim results in October 2020 which indicate that all four treatments evaluated (remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon) had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalised patients. This study is considering evaluating other

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treatments, to continue the search for effective COVID-19 therapies. So far, only corticosteroids have been proven effective against severe and critical COVID-19 infection.[7,8] In July 2020, WHO accepted the recommendation from the Solidarity Trial's International Steering Committee to discontinue the trial's hydroxychloroquine and lopinavir/ritonavir arms.

The International Steering Committee formulated the recommendation in light of the evidence for hydroxychloroquine vs standard-of-care and for lopinavir/ritonavir vs standard-of-care from the Solidarity Trial interim results, and from a review of the evidence from all trials presented at the 1-2 July 2020 WHO Summit on COVID-19 research and innovation. These interim trial results demonstrated that hydroxychloroquine and lopinavir/ritonavir produce little or no reduction in the mortality of hospitalised COVID-19 patients when compared to standard of care. Consequently, Solidarity Trial investigators interrupted the trials with immediate effect.

It is noteworthy that this decision applies only to the conduct of the Solidarity Trial in hospitalised patients and does not affect the possible evaluation in other studies of hydroxychloroquine or lopinavir/ritonavir in non-hospitalised patients or as pre- or post-exposure prophylaxis for COVID-19.

French Study, "Discovery"

France is co-ordinating the Discovery trial to compare the same drugs with standard care in a network of 3,200 patients in Belgium, France, Germany, Luxembourg, the Netherlands, Spain, Sweden and the UK. This will be randomised but non-blinded and will assess outcomes at 15 days.[7,8]

This study is a multi-centre, adaptive, randomised, open clinical trial of the safety and efficacy of treatments of COVID-19 in hospitalised adults. The study is a multi-centre and multi-country trial that will be conducted in various sites in Europe. Adult patient (≥18 year-old) hospitalised for COVID-19 with SpO2 ≤ 94% on room air OR acute respiratory failure requiring supplemental oxygen or ventilatory support are randomised between 4 treatment arms, each to be given in addition to the usual standard of care (SoC) in the participating hospital: SoC alone versus SoC + Remdesivir versus SoC + Lopinavir/Ritonavir versus SoC (this treatment arm has been ceased since June 29, 2020) + Lopinavir/Ritonavir plus interferon ß-1a versus SoC (this treatment arm has been ceased since June 29, 2020) + Hydroxychloroquine (this treatment arm has been ceased since May 24, 2020).

The primary objective of the study is to evaluate the clinical efficacy and safety of different investigational therapeutic options relative to the control arm in patients hospitalised with COVID-19, the primary endpoint is subject clinical status (on a 7-point ordinal scale) at day 15. The secondary objectives of the study are to evaluate: 1) the clinical efficacy of different investigational therapeutic agents through 28 days of follow-up as compared to the control arm as assessed by clinical severity (7-point ordinal scale, national early warning score, oxygenation, mechanical ventilation), hospitalisation, mortality through 28 days of follow-up, in-hospital mortality and 90-day mortality, 2) the safety of different investigational therapeutic options through 28 days of follow-up as compared to the control arm as assessed by the cumulative incidence of serious adverse events (SAEs), the cumulative incidence of Grade 3 and 4 adverse events (AEs), the discontinuation or temporary suspension of antiviral drugs for any reason, and the changes in white blood cell count, haemoglobin, platelets, creatinine, blood electrolytes, prothrombin time and international normalised ratio (INR), glucose, total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) over time.[7,8]

Other agents that have shown potential for the treatment of earlier coronavirus infections SARS and MERS are also being evaluated on the basis that the viruses share structural similarities with SARS-CoV-2. These include novel agents in development and antivirals currently in use for other indications. In addition, several studies have evaluated potential treatments *in vitro*.[9,10,11] A number of these therapies appear to have been introduced in China but are not well reported in English language scientific literature. China, as the country with the longest experience of managing COVID-19, is likely to have valuable expertise to share with the rest of the world.

Following is a summary of various agents under investigation for the treatment of COVID-19 that have shown some promise.[7,8]

1. Chloroquine/hydroxychloroquine: This drug

impairs release of virus after cell entry and blocks virus binding to cell receptor. It modulates immune response. The Food and Drug Administration (FDA) has given emergency use authorisation in the USA, however, the UK Medicine and Healthcare products Regulatory Agency (MHRA) states that it should only be used within a clinical trial. It is being investigated in the WHO SOLIDARITY study. Hydroxychloroquine is the preferred choice as it is associated with fewer adverse effects than chloroquine.

2. Hydroxychloroquine + azithromycin: Hydroxychloroquine impairs release of virus after cell entry and block virus binding to cell receptor. It modulates immune response. Azithromycin possesses possible anti-inflammatory action and it prevents secondary bacterial infection. One trial suggests reduction in viral nasopharyngeal carriage at 6 days in 20 patients as compared with unmatched untreated cohort, with azithromycin reinforcing the effect of hydroxychloroquine.[12]
3. Lopinavir/ritonavir: These agents are viral protease inhibitors. The use of this combination may inhibit SARS-CoV-2 virus and thus reduce adverse outcomes of infection. A randomised controlled trial including 200 patients, suggested no benefit so far.[13] Another trial is now underway in combination with a steroid, dexamethasone. Lopinavir/ritonavir combination is also being investigated in the WHO SOLIDARITY study.
4. Remdesivir: This drug blocks viral RNA synthesis. It has a broad-spectrum of activity against many coronaviruses. It was given emergency use authorisation by the FDA in the USA. Clinical trials have reported preliminary results.[14,15,16] Data from a study called Adaptive COVID-19 Treatment Trial (ACTT) indicates beneficial effect on reduction of time to recovery. Remdesivir is included in the WHO SOLIDARITY study.
5. Tocilizumab: This agent blocks interleukin-6 signalling which may inhibit the cytokine release in cytokine storm during severe COVID-19 infection. COVACTA trial supported by the US FDA is currently studying the role of tocilizumab in patients with severe COVID-19 pneumonia and cytokine storm.[8]
6. Favipiravir + interferon alpha: In this combination, favipiravir blocks viral RNA synthesis and interferon alpha stimulates innate antiviral response. This combination is being studied in a number of trials in China.[10]
7. Favipiravir + baloxavir marboxil: This combination of two antiviral agents blocks viral RNA synthesis. The U.S. Food and Drug Administration has approved baloxavir marboxil for the treatment of acute uncomplicated influenza (flu) in patients 12 years of age and older who have been symptomatic for no more than 48 hours. Now it is being studied against COVID19 in combination with favipiravir.[11]
8. Ribavirin + interferon alpha+ Lopinavir/ritonavir: This is a triple therapy combination of antiviral agents. Ribavirin inhibits the activity of the enzyme RNA dependent RNA polymerase, due to its resemblance to building blocks of the RNA molecules. It may inhibit replication of SARS-CoV-2. Lopinavir/ritonavir combination is viral protease inhibitors which may also inhibit SARS-CoV-2 virus and thus reduce adverse outcomes of COVID-19 infection. Interferon alpha stimulates innate antiviral response. Triple therapy is recommended by National Health Commission of the People's Republic of China as per Guidelines for diagnosis and treatment of novel coronavirus pneumonia 2020 (Trial Version 5).[17]

A trial claiming to show efficacy with hydroxychloroquine plus azithromycin received wide coverage in the lay media.[12] This study had important methodological deficiencies and its conclusions have been disputed by expert reviewers.[18] In addition, this combination is associated with an increased risk of QT interval prolongation which may turn out to be fatal in some high risk patients. Another controlled trial indicated that the combined viral protease inhibitor formulation of lopinavir/ritonavir is ineffective.[13] However, an uncontrolled trial of remdesivir which has *in vitro* activity against SARS-CoV-2, demonstrated improvement in 36 of 53 (68%) COVID-19 patients who were severely ill and who had oxygen saturation at ≤94% or were receiving oxygen support.[14] More recently, a randomised

control study has been published from China including 237 patients,[15] and headline results released from a global phase 3 trial named Adaptive COVID-19 Treatment Trial (ACTT) including 1063 patients.[16] Both of these studies included significant numbers of hospitalised patients with COVID-19 pneumonia.

In the study from China, remdesivir did not reduce time to clinical improvement, however, there was a trend towards faster improvement in patients who had a duration of symptoms of 10 days or less. By contrast, the ACTT study suggested that treatment with remdesivir was associated with a more rapid recovery as compared with placebo.[16] Median time to recovery was 11 *vs* 15 days, p<0.001, and there was an overall trend towards improved mortality (8.0% *vs* 11.6%; p=0.059). More data is required to provide a clearer picture on the benefits of remdesivir in rapid recovery and improved mortality from COVID-19.

The role of adjunctive agents such aspirin in severe COVID-19 infection with pneumonia has also been evaluated. A recent study indicated that hospitalised patients with COVID-19 who received aspirin prior to hospital admission or within 24 hours of hospital admission had a significantly lower risk of complications and death compared with patients who did not receive aspirin. [19] Aspirin use had a crude association with less mechanical ventilation (35.7% vs 48.4%; P = .03) and reduced intensive care unit admission (38.8% vs 51.0%; P = .04), but no crude association with in-hospital mortality (26.5% vs 23.2%; P = .51). Two of the most significant events in the pathophysiology of SARS-CoV-2 virus infection are cytokine storm and micro clot formation. The beneficial effects of aspirin in severe COVID-19 infection are believed to be blood thinning action and prevention of micro clot formation. The conclusion of this study was that aspirin use may be associated with improved outcomes in hospitalised COVID-19 patients.[19] However, sufficiently powered randomised controlled trials are required to elucidate the causal relationship between aspirin use and reduced lung injury and mortality in COVID-19 patients.

Conflict of Interest

The authors confirm that they have no conflict of interest.

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ORIGINAL ARTICLE

Knowledge and Attitude of Healthcare Workers to Predict the Confidence Level to Combat Covid-19

Hamzullah Khan,[1] Faridullah Shah,[2] Shehzadi Neelum,[3] Muhammad Zakir[4]

ABSTRACT

Objectives: To determine the knowledge and attitude of healthcare workers about COVID-19 pandemic to predict the confidence level to face the pandemic.

Study Design: Cross sectional study.

Place and Duration of Study: The study was conducted from 1st March 2020 to 30th March 2020 in Medical Teaching Institute, Qazi Hussain Ahmed Medical Complex Nowshera, and an affiliated teaching hospital of Nowshera Medical College.

Material and Methods: A total of 158 participants were selected via convenient sampling, irrespective of age and gender. A pre-validated questionnaire was administered to assess the knowledge and attitude of the respondents about COVID-19 pandemic. Relevant information's were collected and data was entered in SPSS version 25 for descriptive and regression analysis to assess the knowledge and attitude of healthcare providers towards COVID-19.

Results: Eighty one (51.3%) were males and 77(48.7%) females. The age was from 20 to 50 years. The distribution on basis of education was; 57(36.1%) medical students, 33(20.9%) General practitioners, 29 (18.6%) Bachelor degree holders and 35(22.2%) with post graduate qualification in medicine. We observed a significant difference in male gender (vs female gender*)* regarding; knowledge of outbreak *(p=0.002,OR: 7.2),* biology of 2019-nCoV*(p=0.07,OR: 3.37),* worries about the shortage of food in lock down situation*(p=0.005,OR: 4.1)* and confidence level *(p=0.07,OR: 4.2).* A significant difference was observed in population groups based on education levels regarding; treatment approach *(p=0.001),* denial of biological war *(p=0.001)* and government role in pandemic in provision of health care *(p=0.001).* A significant difference in opinion was noted in different age group regarding; food shortage in lockdown *(p=0.005, OR: 4.1)* and level of confidence *(p=0.07, OR: 4.2).*

Conclusion: Healthcare workers have sufficient knowledge about COVID-19 pandemic, its prevention, precautionary measures during the rapid rise period of outbreak. The approach towards treatment options and denial of misconception like biological war, is more positive in educated group having medical qualification.

Key Words: *COVID-19, Knowledge and Attitude, Pandemic, Regression Analysis.*

Introduction

According to the World Health Organization, the viral diseases continue to emerge and are representing serious health issues in time and future. In 2002-03 world experienced outbreak of Sever Acute Respiratory Distress Syndrome (SARS) and H1N1 (Homophiles Influenza) in 2009, Middle East Respiratory Syndrome (MERS) in Saudi Arabia in 2012 and Corona Virus disease (COVID) in 2019.[1] The outbreak in 2019 was totally different with presentation of pneumonia of unknown cause, later on the Chinese Centre for Disease Control and Prevention and local CDC attributed it to a novel virus belonging to corona family and was termed as 2019-nCoV.[2]

Corona Virus disease termed as COVID-19 is an emerging highly contagious respiratory disease that is caused by novel corona virus. It was first reported from Wuhan China in December 2019. Its main clinical symptoms are fever, dry cough, fatigue, myalgia and dyspnea.[3] Case fatality rate of 2.3% has

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been reported from china that is lower than SARS (9.5%) , MERS (34.4%) and H7N9 (39%).[4] In Pakistan the literature so for covering the prevalence and incidence is deficient, however the so far reported data from government sources declares 4000 confirmed cases with 54 deaths. Punjab is the province with the highest number of corona cases reaching 2000.[5]

People adherence to preventive and precautionary measures is essential, which largely depends on the knowledge, attitude and practice of people toward COVID-19 in accordance with KAP theory.

Italy, the second most affected country, with 888 cases of SARS-CoV infection with history of travel to the epidemic area were initially reported in Lombardia and Veneto regions. They attributed these infections with poor compliance of the people towards precautionary measures during the early stages of current epidemic in the country.[6] The levels of understanding and the importance of isolation and social distancing are the key to contain this virus. That demands for the execution of a survey in our population to determine the preparedness of our population for the pandemic that has almost hit our country. Present study was therefore designed as to assess the knowledge and attitude of the regarding the pandemic to predict the confidence level to face the pandemic.

Material and Methods

A quantitative cross-sectional research design was utilized in March, 2020. This study was conducted in Medical Teaching Institute, Qazi Hussain Ahmed Medical Complex Nowshera, an affiliated teaching hospital of Nowshera Medical College. A sample size of 158 was calculated through Raosoft[7] an online sample size calculator, with confidence interval of 95%. Ethical approval was obtained from the institutional ethical review board of Nowshera Medical College via Notification No- 77/NMC/IRB dated 6th Feb 2020, before the execution of the survey. Prior informed consent was obtained from all the respondents and they were assured of confidentiality. The convenient sampling techniques was used for the present study. All the respondents irrespective of age and gender with minimum qualification of bachelor degree. Respondents with qualification less than bachelor degree were excluded from the study with an exception for 4th year medical students of Nowshera Medical College that were included in the study.

A pre-validated questionnaire comprising 13 items, were administered. A total of 158 of the respondents were assessed for their knowledge and attitude regarding COVID-19. The questionnaire had three parts. There were pre-requisite demographic information of the respondents regarding their name, age, email, qualification and nature of employment.

Part 1. Information about the knowledge of the respondents about COVID-19 biology, transmission, precautions, treatment options and preventive measures.

Part 2. Information about the responders' contacts with Covid-19 infected patients, testing method and place, treatment, isolation and quarantine and other related issues.

Part 3. Information about the lockdown, necessities for lockdown, worries about the situation and handling is food shortage and health issues and confidence level in this situation.

The questionnaire was distributed though email and in hard copies and the responders were given option to submit it via email or by hand.

Data was entered in SPSS version 25 for descriptive analysis and correlation analysis. There were two types of categorical variables in the study, one ordinal variable like age and education level of the respondents. Second were nominal variables like gender and opinion of the respondents (Yes/No) for assessing their knowledge and attitude. Frequency and percentage were calculated for categorical variables. Binary logistic regression analysis was used to predict the relationship of knowledge and attitude of the respondents with different outcomes of the pandemic wave and further to predict the level of satisfaction based on their knowledge and attitude to combat COVID-19.

Results

A total of 158 respondents were included in the study. The categorization based on age, gender and qualification is shown in table I.

A significant difference was noted among gender groups using binary logistic regression analysis for different variables to predict the confidence level based on their knowledge and attitude as mentioned in Table II.

The male gender reported to be more confident with their religious believes, precautions and level of awareness and cleanliness would help them to pass thorough this crucial time successfully as compared to their counterparts*(p=0.07,OR: 4.2)* (Table II).

It was found that difference in age groups were significantly associated with difference in Knowledge about 2019nCoV Biology *(p=0.002, OR*: 7.3) and in treatment approaches (p=0.017). Likewise the level of confidence in present wartime was more in elderly age group as compared to the youngsters (p=0.008). (Table III).

Moreover a significant difference in treatment approach was noted in different groups based on education *(p=0.001).* Based on strategic and geopolitical conflicts, sometimes it is correlated that COVID-19 is not a disease rather a biological war that was denied by the group with postgraduate qualification in medicine *(p=0.001, OR: 23).* The Odds ratio of 23 documents a strong denial of COVID-19 being a biological war.

Table I. Demographic information of the respondents

Gender Distribution			
	Frequency	**Percent**	**Cumulative Percent**
Male	81	51.3	51.3
Female	77	48.7	100.0
Total	158	100.0	
Age Groups			
	Frequency	**Percent**	**Cumulative Percent**
20-30	82	51.9	51.9
31-40	68	43.0	94.9
41-50	8	5.1	100.0
Total	158	100.0	
Education Level of the Respondents			
	Frequency	**Percent**	**Cumulative Percent**
Undergraduate (4th year MBBS Students NMC)- The pioneer class of NMC	57	36.1	36.1
Bachelor degree	29	18.4	54.4
Master, M.Phil	24	15.2	69.6
FCPS/Fellowship	11	7.0	76.6
MBBS-Professional	33	20.9	97.5
Technicians/Nurses	4	2.5	100.0
Total	158	100.0	

Table II. Regression Analysis of Gender Group with Different Variables in Assessing KAP of the Respondents towards COVID-19

S.No		B	S.E.	Wald	df	Sig.	Exp(B)
1	Outbreak information	1.974	0.635	9.681	1	0.002	7.202
2	COVID-19 Biology	1.215	0.672	3.269	1	0.071	3.37
3	Treatment Information	0.008	0.614	0	1	0.989	1.008
4	Risk factors information	-22.987	232.424	0	1	0.999	0
5	Information on importance of isolation	-21.903	142.368	0	1	0.999	0
6	Is it Biological war?	-0.501	0.491	1.038	1	0.308	0.606
7	Government should provide food and health facility in lock down	0.472	0.514	0.844	1	0.358	1.604
8	Can you work from home?	0.354	0.438	0.651	1	0.42	1.424
9	Do you afraid of food shortage in lockdown?	1.414	0.508	7.748	1	0.005	4.111
10	Have alternate source of income in Lock down situation	0.148	0.649	0.052	1	0.82	1.159
11	Have any relief from Government in this situation	3.158	0.906	12.147	1	0	23.523
12	What keeps u confident	1.453	0.537	7.329	1	0.007	4.275
13	What is more important for you and your family in lockdown	1.584	1.005	2.486	1	0.115	4.874

Discussion

Knowledge is a key to success, the more you know about a disease the more easily it can be managed to reduce morbidity and mortality. KAP strategy is an important tool to assess the preparedness level and to predict the confidence level of the community to combat COVID-19. In present study an acceptable amount of knowledge about the outbreak was noted in different gender groups *(p=0.002, OR: 7.2.* The male population dominated in knowledge about the biology of 2019nCoV *(p=0.07, OR: 3.37).* Female

Table III. Regression Analysis of Age Categories with Different Variables in Assessing KAP of the Respondents towards COVID-19

S.No		B	S.E.	Wald	df	Sig.	Exp(B)
1	Outbreak information	0.608	0.586	1.075	1	0.3	1.837
2	COVID-19 Biology Information	1.988	0.638	9.706	1	0.002	7.303
3	Treatment Information	-1.416	0.593	5.71	1	0.017	0.243
4	Risk factors information	20.303	232.423	0	1	0.999	0.886
5	Information on importance of isolation	16.858	142.358	0	1	0.999	0.415
6	Is it Biological war?	0.84	0.536	2.46	1	0.117	2.317
7	Government should provide food and health facility in lock down	0.042	0.514	0.007	1	0.936	1.042
8	Can you work from home?	0.571	0.451	1.602	1	0.206	1.769
9	Do you afraid of food shortage in lockdown?	-0.941	0.497	3.583	1	0.058	0.39
10	Have alternate source of income in Lock down situation?	-2.155	0.625	11.875	1	0.001	0.116
11	Have any relief from Government in this situation?	-1.436	0.765	3.523	1	0.061	0.238
12	What keeps u confident?	-1.31	0.565	5.371	1	0.02	0.27
13	What is more important for you and your family in lockdown?	-0.453	0.884	0.263	1	0.608	0.636

population and respondents of younger age group were more worried about the food and health issues in lock down situation during the pandemic. In the same way the level of education significantly differed in term of treatment approaches and precautionary measure *(p=0.001),* denial of biological warfare *(p=0.001)* and in the opinion that government should provide food and health facility in lock down to the incumbents. China has successfully achieved desired results by their impared knowledge, attitude and practices towards COVID-19.[8]

Zhong BL et alalso reported a significant difference in knowledge score regarding COVID-19 of male vs female gender (*OR: 0.81, P<0.001*) that matches our findings.[9] The China is expected to have won the battle due to their level of basic knowledge about the disease. They used KAP strategy in the SARS and COVID-19 epidemic where about 90% of the residents believed that they know the disease, how to prevent and what precautionary measures need to be taken [10, 11.]In our society male is earning live hood for family. High exposure risk of male population indirectly increases the chances of infection with COVID-19.[12]

Similarly the younger the age the more is stigma/fear of food shortage and healthcare issues during the lockdown *(p=0.005, OR: 4.1).* It has been observed that younger age people especially the students, are at a higher risk to SARS-Cov-2 infection because of their frequent exposure to crowded places for study and other activities of their choice.[13] So, the students have a strong fear of consequences of lockdown as compared to the elderly population.

The confidence level of male population to fight the pandemic was more than female gender *in present study.* Zhong BL et al[9] have also observed that the majority (90.8%) of the participants in their study were optimistic to get succeeded in winning the war against corona virus, that strongly correlates our findings. Studies from China have reported that education level of clients increases the confidence 3- 5 times more to win the battle against COVID-19, *(OR: 3.13-5.04, P<0.001)* that matches our findings [9,14].

Studies from China have reported that there is no evidence of bio-warfare associated with COVID-19 pandemic. It has been clarified in the research papers published, that the outbreak in the city of Wuhan was a natural epidemic and not part of any warfare, that supports our findings regarding the denial of biological war.[3,15]

The findings of our KAP are similar in outcome and statistics of the Zhong BL et al[9.] Saudi Arabia also succeeded to the maximum to combat the pandemic and to safeguard their citizens and the pilgrim by ensuring public adherence to preventive measures that was influenced by their knowledge and attitude toward COVID-19 which is closely in concordance with our findings.[16] In china the residents' attitudes and practices towards COVID-19 proved fruitful in

winning the battle against COVID-19. But like our findings the attitude towards confidence of winning significantly differed across categories of gender, age and education ($P<0.05$)[9] that matches our findings. The limitation of this study was limited number of the respondents that make us cautious in generalizing these findings to the populations of the district as it was selected in one setting/Hospital/ institution. Future studies should focus on the subject matter with large population with representation of all sectors to have a better outcome to predict/suggest the findings for decision making by the higher authorities to prevent disastrous pandemic. It is further suggested that healthcare workers should understand the basics of 2019nCoV, its clinical presentation and precautionary measures to contain virus and to avoid its spread in general community.

Conclusion

Healthcare workers have sufficient knowledge about COVID-19 pandemic, its prevention, precautionary measures during the early outbreak across the country. Female gender is more worried about the shortage of food in case of lockdown.

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ORIGINAL ARTICLE

Diagnostic Accuracy of Doppler in Identifying Malignant Ovarian Neoplasms Taking Histopathology as Gold Standard

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ABSTRACT

Objective: To determine the diagnostic accuracy of Color Doppler and Spectral Doppler in identifying malignant ovarian neoplasm using histopathology as the gold standard.

Study Design: Cross section validation

Place and Duration of Study: The study was carried out in Radiology Department in collaboration with the Pathology department at Rawalpindi Medical University and Allied Hospitals, Rawalpindi, for a period of 11 months, from May 2015 to April 2016.

Material and Methods: Patients with a clinically palpable ovarian mass or ovarian masses detected incidentally on gray scale ultrasound, who underwent surgery or biopsy within one month of Doppler examination were selected by consecutive (non-probability) sampling. A total of 153 patients were then examined by Duplex ultrasonography. Flow score, Resistive index (RI) and Pulsatility index (PI) were recorded for each patient. Post-surgical histopathology of the excised ovarian mass or tissues as benign or malignant was collected and diagnostic efficacy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of Duplex USG in identifying malignant ovarian neoplasms was calculated.

Results: Diagnostic accuracy of Doppler ultrasound in identifying malignant ovarian neoplasm has been calculated as 95.4%, sensitivity 86.2%, specificity 97.58%, positive predictive value 89.28% and negative predictive value 96.8% in comparison with the gold standard of histopathology.

Conclusion: The study concludes that Doppler ultrasound is a reliable and dependable technique in the diagnosis of malignant ovarian neoplasm, however though Doppler parameters have good accuracy histopathology remains the gold standard due to limitations of the Doppler modality in pelvic inflammatory lesions.

Key Words: *Biopsy, Doppler Ultrasound, Malignant Ovarian Neoplasm, Pulsatility Index, Resistive Index.*

Introduction

Ovarian malignancy is the third most common gynecological malignancy after cervical and uterine cancer, being 7th most common malignant tumor amongst women.[1] One in every 75 women is at risk of developing ovarian malignancy and one in every 100 women with ovarian cancer dies.[2] Incidence of ovarian cancer increases with advancing age whereas multiparty and early age at first birth, are associated with lower risk. Positive personal or family history of breast or ovarian cancer also increases the risk of developing ovarian malignancy.[1,2] Preoperative classification of ovarian masses, particularly to identify malignant mass, is extremely helpful in optimal patient management with minimum morbidity.[3] Good and reliable preoperative assessment of ovarian tumors with confident identification of malignancy helps in appropriate referral of women to gynecologic oncological care and women with benign disease for conservative management or surgery.[4]Conventional gray scale 2D ultrasound or even color Doppler is sometimes unable to differentiate between benign or malignant neoplasms or inflammatory / infective masses or physiological self-limiting corpus luteal hematomas which generally do not need surgical or medical treatment unless except in rare occurrence of hematoma rupture.[4,5] Clinically these tumors may be asymptomatic, incidentally seen on routine ultrasound examination or patient may present with acute emergency like torsion or rupture of a mass.[3,4,5]

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Doppler ultrasound uses sound waves to detect blood flow hence it is considered to be an effective modality to detect malignant masses as malignant neoplasm show prominent flow signals on color doppler likely due to neo angiogenesis, in contrast to benign lesions.[3,6] The color content of the tumor probably reflects tumor vascularity better than any other Doppler parameter.[3] A color score is assigned to describe the amount of blood flow within the tumor: color score 1 being no detectable blood flow; score 2 to a minimal flow; score 3 with moderate flow; and color score 4 to a highly vascular mass.[7]Benign lesions show peripheral color flow whereas malignant lesions exhibit color flow at the periphery of the mass, as well as central, intra-lesional, septal and solid intra tumoral flow.[7] The neo angiogenesis within a malignant mass are made up of abnormal vessels, without any regulated blood flow. These new formed vessels have no smooth muscles within their walls and also contain multiple arteriovenous shunts. Therefore a malignant mass shows low-impedance flow (low pulsatility index < 1.0) and (low resistance index < 0.4).[6,7] Study by Prasad et al concluded that analysis of color flow data as a predictor of malignancy had a sensitivity of 100% and negative predictive value of 100% while specificity and positive predictive value were 80% and 36% respectively.[7] In one study, 92.59 % of malignant tumors showed RI less than 0.6 in contrast to only 9.09 % of benign tumors.[8] Studies also indicate that raised serum levels of ovarian tumor markers for example CA-125 are also associated with malignancy, but recent studies suggest Doppler assessment to be superior in discriminating benign and malignant ovarian neoplasms.[2] Absence of color flow seems to be accurate for labeling a mass as benign and exclude any malignancy, but some misdiagnosis may occur in cases of metabolically active benign masses like inflammatory lesions or tubo-ovarian abscess. However, spectral Doppler along with color flow is useful in identifying malignant ovarian neoplasm. Vaginal and per abdominal gray scale and Doppler ultrasound (Duplex scan), along with serum CA-125 levels, family history and genetic history (BRCA-1, BRCA-2) may aid in early diagnosis of ovarian cancer but various research projects are still in process.

A thorough search of the literature revealed that there has not been much work done on the preoperative identification of malignant ovarian tumor with respect to Pakistani population. The simple Doppler USG parameter of resistive index is not studied much locally or internationally due to recent development of expensive and time consuming cross sectional imaging. This study was an effort to determine the diagnostic accuracy of Color Doppler and Spectral Doppler in identifying malignant ovarian neoplasm in Pakistani population using histopathology as the gold standard.

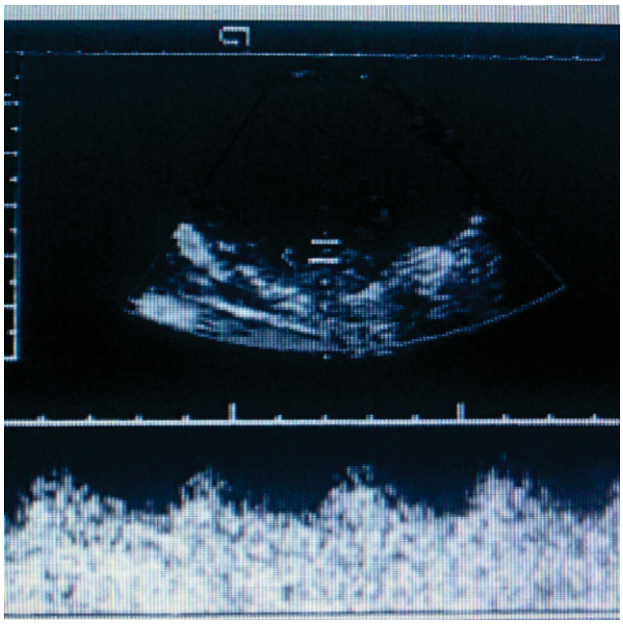

Fig 1: Cystic Mass with Papillary Projection Showing Low Resistant Spectrum Having Ri of 0.23 which came out to be Serous Cystadenocarcinoma on Histopathology

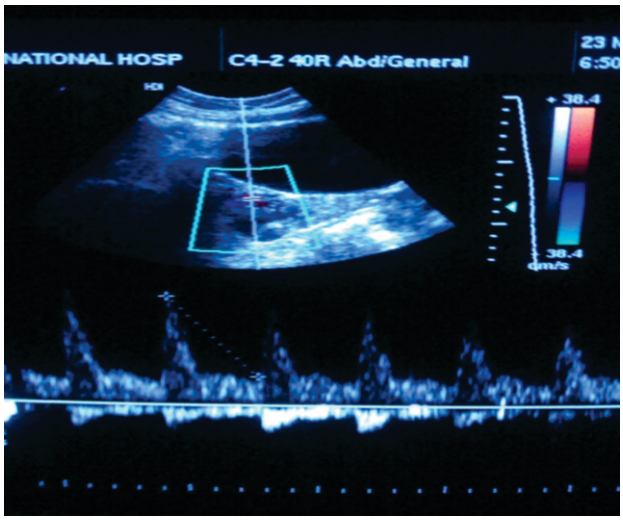

Fig 2: Solid cum Cystic Mass Showing High Resistive Spectrum and RI of 0.72. On Histopathology, It Came Out To be a Fibroma

Material and Methods

After approval by the Ethical Committee cross sectional validation study was carried out. The study was conducted in the Radiology Department in collaboration with the pathology department at Rawalpindi Medical University and Allied Hospitals, Rawalpindi. The study was carried out for 11 months, from May 2015 to April 2016. The study population comprised 153 patients with ovarian mass, selected by consecutive (non-probability) sampling; either detected incidentally on gray scale ultrasound or referred from gynecology department for USG Doppler study to Radiology Department Rawalpindi Medical University and Allied Hospitals, Rawalpindi. An informed consent was taken and then patient was subjected TOSHIBA NEMIO XG (TA 312) real time Ultrasound and Doppler scanner. 3.75 MHZ sector curvilinear transducer was used by trans-abdominal approach, and B Mode ultrasonography, Color Doppler and Spectral Doppler of patient was performed by the resident doctor and findings were confirmed by the consultant. The lesion was analyzed at high sensitivity settings with lowest pulse repetition frequency without aliasing. Three readings each of Pulsatility Index (PI) and Resistive Index (RI) values were calculated and the lowest PI and RI were recorded. Patient was then referred back to the gynecologist. Those patients who underwent surgery or biopsy within one month of Doppler examination were only included in the study. Excised ovarian mass or tissues were evaluated by team of consultant histopathologists in Pathology department, Rawalpindi Medical University and Allied Hospitals, Rawalpindi. Histopathologists had no prior information of the doppler findings. Histopathology results were directly obtained from the pathology department through patient's hospital admission number. Doppler USG results were compared to histopathological results for confirmation of malignancy. The data was collected with the help of proforma attached and diagnostic efficacy, sensitivity, specificity, positive predictive value and negative predictive value of Doppler in identifying malignant ovarian neoplasms were calculated by a 2 X 2 table. Data was entered and analyzed in SPSS version 10. Descriptive statistics were calculated for both qualitative and quantitative variables. For qualitative variables like marital status, parity and intra tumoral color flow, frequency / percentages were calculated and for quantitative variables like age, PI and RI, mean and +/- SD were calculated.

Results

This was a cross sectional validation study conducted on 153 patients. All were female, who were referred for Duplex ultrasound to evaluate clinically detected abdominopelvic mass or incidental ovarian mass or masses, on gray scale ultrasound, (Irrespective of their age or menstrual status). The study population was in the age group 10 to 65 years. Out of the total sample of 153, married women were 111 (72.5%) and unmarried women were 42 (27.5%). 49 (32%) had 0 parity, 10 (6.5%) had 1 parity, 31 (20.3%) had 2 parity, 36 (23.5%) had 3 parity, 20 (13.1%) had 4 parity, 5 (3.3%) had 5 parity and 2 (1.3%) had 6 parity. The mean parity was 1.94 with a standard deviation of +/-1.619. Demographic characteristics of patients are briefly summarized in table I, as under;

Table I: Demographic Characteristics of Patients with Ovarian Carcinoma (N=153)

No	Characteristics	No. of patients (N)	Percentage %	Mean/Median (SD)
I	Age (Years)	153		34.5 +/- 11.802
II	Age Group (Years)			
	11 to 20	21	13.7	
	21 to 30	44	28.8	
	31 to 40	42	27.5	
	41 to 50	27	17.6	
	51 to 60	17	11.1	
	61 and above	2	1.3	
III	Marital Status			
	Married			
	Unmarried			

Calculations according to 2 x 2 table from the data collected, as shown in Table II

Table II: Diagnostic Accuracy of Doppler in Identifying Malignant Ovarian Neoplasm Taking Histopathology as Gold Standard (N=153)

Color Doppler and Spectral Doppler	Histopathology Malignant	Histopathology Benign
Malignant	True Positive a) 25	False Positive a) 3
Benign	False Negative b) 4	True Negative c) 121

- **Sensitivity** a / a + c x 100 = 25/25+4 x 100 = 86.2 %
- **Specificity** d / b + d x 100 = 121/3+121 x 100 = 97.58 %
- **Positive predictive value (PPV)** a / a + b x 100 = 25/25+3 x 100 = 89.28%
- **Negative predictive value (NPV)** d / c + d x 100 = 121/4+121 x 100 = 96.8 %
- **Diagnostic Accuracy** a + d / a + b + c + d x 100 = 25+121/25+3+4 +121 x 100 = 95.4 %

Statistical analysis of the current study revealed that overall diagnostic accuracy of Doppler ultrasound in identifying malignant ovarian neoplasm is 95.4% which is comparable with gold standard histopathological biopsy. Sensitivity was found to be 86.2% and specificity 97.58%. Positive predictive value was 89.28% and negative predictive value was calculated to be 96.8%.

Discussion

Doppler ultrasonography is noninvasive, cost effective, reliable and dependable technique with acceptable diagnostic accuracy for effective preoperative classification of malignant ovarian disease, helping the clinician to decide the management of the disease and extent of surgery in case of malignancy. A study by Khalaf et al, recently demonstrated that color flow Doppler shows neo-vascularity in 88.7% of the malignant lesions, 73.6% of them has central blood flow in contrast to only 1.9% central flow in benign lesions. They also stated that the diagnostic performance of RI < 0.6 was higher.[9]The current study used a cut-off criteria of PI < 1 and RI < 0.4, to optimize the study in terms of sensitivity and specificity, 86.2% of malignant tumors showed RI < 0.4 and PI < 1, and in contrast only 13.8% of benign tumors demonstrated RI value < 0.4 and PI value < 1. Thus for identification of malignant lesion by Doppler indices, the sensitivity of RI and PI was 86.2% and specificity of 97.58%. However another local study reported different results, Majeed H et al reported in 2011 a sensitivity of only 18.18%, specificity of 84.61% and diagnostic accuracy of 64.86%, taking a threshold of 0.4 for RI.[10] This could be explained by newer USG machines having better resolutions with per abdominal approach. [11]However investigations to compare doppler parameters of an ovarian mass by per abdominal and trans-vaginal approach are further in plan.

Doppler has no radiation exposure and side effects as compared to other modalities; histopathology still remains the gold standard due to limitations of the Doppler modality in benign inflammatory or infective lesions which may increase local blood flow and reduce resistive index mimicking neo-vascularization in malignancy as also observed in 2 false positive cases of tubo-ovarian abscess and 1 false positive case of rupture corpus luteal cyst hematoma in current study. Ultrasound detects and identifies most of these as physiological cysts, which are not an indication for surgery. Physiological cysts include simple cysts with no internal septations or any solid component; for example follicular and corpus luteal cyst but occasionally these adnexal cysts may have low Doppler indices (low RI and PI) and this may decrease the specificity of our RI and PI measurements.

Our results are similar to other recent reports, which emphasize that although malignant lesion shows abundant vascularization with low resistance flow but some benign lesions (e.g. tubo-ovarian abscesses and chocolate cysts (endometriomas) may also show this pattern which affected the results. Khurana et al reported in 2016 that Color Doppler showed increased vascularity in 100% of malignant tumors in contrast to only 54.24% of benign tumors. [12]Vice versa, a malignant lesion could have multiple vascularized areas with variable neo angiogenesis and hence variable flow resistance.[13] In order to reduce these biases, all aspects of the lesions are to be evaluated with thorough spectral analysis of all the vascularized areas within the lesion to calculate minimum RI for detecting malignancy. Another limitation of our study was that comparisons between different radiological modalities like CT and MRI is not drawn which is in plan to explore in further studies. Mathieu et al suggested that sensitivity and spatial resolution of ultrasound is generally better than CT /PET CT but MRI has reported greater accuracy and specificity in the diagnosis of malignant adnexal masses 89% and 84%, respectively, compared to USG having 64% and 40% respectively but they didn't study doppler parameters along with gray scale 2D USG and our study revealed doppler USG has better accuracy (97.5%) and specificity (95.4%) as compared to MRI. High cost and lower availability of cross sectional imaging and MRI, is another reason for not being the first-line imaging modality for the evaluation of adnexal masses.[14]Ormsby et al concluded that concomitant use of serial CA-125 as in the ROCA model should also increase the positive predictive value of detecting malignancy compared with USG and Doppler alone. Our study revealed a PPV of 89.2% of doppler USG alone.[15] Furthermore, evaluation of Doppler USG along with serial CA-125 levels is in plan to discriminate between benign and malignant adnexal

masses. Despite these limitations, results of our study compared to the various studies were found supportive of each other, so imparting deeper insight into the diagnostic modalities of ovarian neoplasm. This would help in the future in building confidence for successful and accurate diagnosis and to monitor the patients with this disease.

Conclusion

The study concludes that Doppler ultrasound is a reliable and dependable technique in the diagnosis of malignant ovarian neoplasm, however though Doppler parameters have good accuracy histopathology remains the gold standard due to limitations of the Doppler modality in pelvic inflammatory lesions or infective lesions which may increase local blood flow and reduce resistive index mimicking malignancy.

Conflicts Of Interest Statement and Funding

The study was conducted in public sector hospital attached to medical university. There were no sponsors involved in the study. Authors state that they have no conflicts of interest to disclose.

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ORIGINAL ARTICLE

Preventive Effect of Turmeric against Anti-Mosquito Smoke Induced Pulmonary Fibrosis in Laboratory Rat

Saira Jawed,[1] Wafa Omer[2]

ABSTRACT

Objective: To appraise the preventive effect of turmeric on anti-mosquito coil smoke induced interstitial fibrosis in lungs of Sprague Dawley rats.

Study Design: Randomized control trial.

Place and Duration of Study: This study was completed in 10 months from 1st August 2014 to 28th May 2015; conducted at Islamic International Medical College, Rawalpindi and National Institute of Health (NIH), Islamabad, Pakistan.

Material and Methods: Three equal groups of 21 adult albino rats were made. Control Group X was retained in fresh air. Experimental Groups M & T inhaled Mosquito Coil smoke for 12 weeks. Group T also had oral turmeric 300mg/kg body weight. After 12 weeks rats were dissected, and their lung tissues were studied microscopically for the presence of fibrosis.

Results: Interstitial Fibrosis was markedly present in the histological sections of lung tissues from experimental group M showing thickened fibrotic alveolar walls and inflammatory cell infiltrate with reduced air spaces in all animals (100%) in group M. Fibrosis was present in 2 out of 7 rats in group T showing a significant protection with only 28.5% of animals with fibrotic lungs. No interstitial fibrosis (0%) was seen in the lung tissues of animals in control group X; all 7 rats showed well-formed alveoli.

Conclusions: Interstitial lung fibrosis caused by Anti-Mosquito coil smoke can be protected with the use of turmeric.

Key Words: *Covid-19, Curcuma, Mosquito Coil, Pulmonary Fibrosis, Turmeric.*

Introduction

Modern medicine to a large extent has failed in its ambition to control both acute and chronic diseases. Traditional herbal medicines have been found effective for the treatment and prevention of several diseases. Turmeric is a traditional herbal medicine.[1] It's broad reaching mechanism of action and lack of systemic toxicity may make it best suited as an adjuvant therapy for various viral and other respiratory disorders like tobacco smoke induced epithelial damage and acute lung injury that are resistant to currently available therapies.[2] Several diseases have been found to have inflammatory origin. Turmeric is safe, affordable and efficacious nutraceutical. Turmeric has significant anti-inflammatory and anti-oxidant properties.[3] It has gained value as a digestive aid, treatment for fever, wounds, infections and blood disorders. Data from animal and pharmacological studies also supports that active ingredients in turmeric play a protective role in various diseases like acute respiratory distress syndrome, chronic obstructive pulmonary disease and allergic asthma and also have proven antiviral properties against para-influenza type 3, respiratory syncytial virus and herpes simplex virus,[4,5,6] its therapeutic action is based on the inflection or prevention of oxidative stress and inflammation confirmed with the studies done at molecular & cellular levels.[7,8] The findings in these researches give substance to the possibility of testing turmeric for the prevention of pulmonary fibrosis caused by allethrins released from burning anti-mosquito coils. Mosquitoes and the transmission of the mosquito borne diseases have been historically controlled by the use of chemical insecticides and mosquito repelling agents like anti-mosquito coil containing Pyrethroids (allethrins), which play a central role in

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mosquito control programs.[9] More toxic products having higher concentration of allethrins are predominating the market due to the rapid spread of resistance worldwide.[10] The use of allethrins in higher concentrations and a complicated mixture of metallic vapors to tackle the resistant mosquitoes, exposes the consumer to a severe health risk.[11] It has already been addressed in the literature that exposure to mosquito coil smoke can have toxic effects on the lungs and can induce histopathological changes like severe emphysema, hyperplasia, chronic obstructive pulmonary disease, edema, hemorrhage & fibrosis, necrosis, hyperemia, connective tissue infiltration by inflammatory cells and obstruction by hyaline material within the lung tissue.[12,13]

The objective of the current research was to demonstrate the efficacy of turmeric in preventing pulmonary fibrosis as there is insufficient literature on the preventive characteristics of turmeric against anti-mosquito allethrins present in coil smoke.

Material and Methods

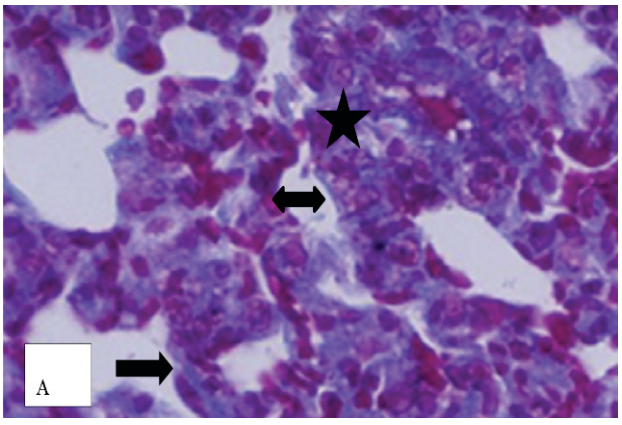
This randomized control trial conducted at Islamic International Medical College, Rawalpindi and National Institute of Health (NIH), Islamabad and was completed in 10 months. A total of 21 Sprague Dawley male rats weighing 250-300g were purchased from the animal house of National Institute of Health (NIH) Islamabad and were randomly divided into three groups; control group X and experimental groups M & T. The study was performed after an ethical approval from the Institutional Review Committee of Riphah International University. Female rats and the rats having a weight of less than 250 g or having a physical disability were excluded from the study. Groups M & T rats were placed in smoke exposure cabins at a temperature of 27±3ºC with a 12hr light/dark cycle along with standard laboratory diet and water. Experimental groups were exposed to mosquito coil smoke for 7 hours per day for 12 weeks; group T received 300mg/kg body weight oral turmeric as well. All rats were sacrificed at the end of 12 weeks and left lungs of all were dissected out and preserved in 10% formalin. After tissue processing slides were prepared and stained with Masson's Trichrome to be studied microscopically first at low power, x10, and then at high power, x40 objective. The histological slides were interpreted by the pathologist. Slides were studied for presence of interstitial fibrosis. Masson's Trichrome stained collagen fibers causing thickening of alveolar septa & alveolar spaces filled with proteinaceous fluid and inflammatory cell infiltrate causing reduction in alveolar spaces was taken as a criterion for interstitial fibrosis.

Results

The lung tissue of all rats (100%) in group M (Fig 2A) had a Masson's trichrome stained dense fibrous connective tissue with collagen fibrils & thickening of alveolar walls with cellular infiltration, proliferation & airspaces filled with proteinaceous fluid. The interstitial infiltrate consisted of lymphocytes, plasma cells, mast cells and eosinophils resulting in interstitial fibrosis. Interstitial pulmonary fibrosis was present in 2 out of 7 rats in group T; thus rats in group T showed a remarkable protection from pulmonary fibrosis with only 28.5% of animals developing fibrosis (Fig 2B). The result is shown in table (Fig 1). The Masson's Trichrome stained histological slides from the rats in control group X had normal honeycomb like alveolar structure with well-formed alveolar walls (Fig 2C).

Table I: Table representing percentage of interstitial lung fibrosis in control and Experimental Groups

Groups (Total rats 21 ; 7 rats in each group)	Interstitial fibrosis		
	Present	Absent	Presence of fibrosis (percentage)
Group X	0	7	0%
Group M	7	0	100%
Group T	2	5	28.5%



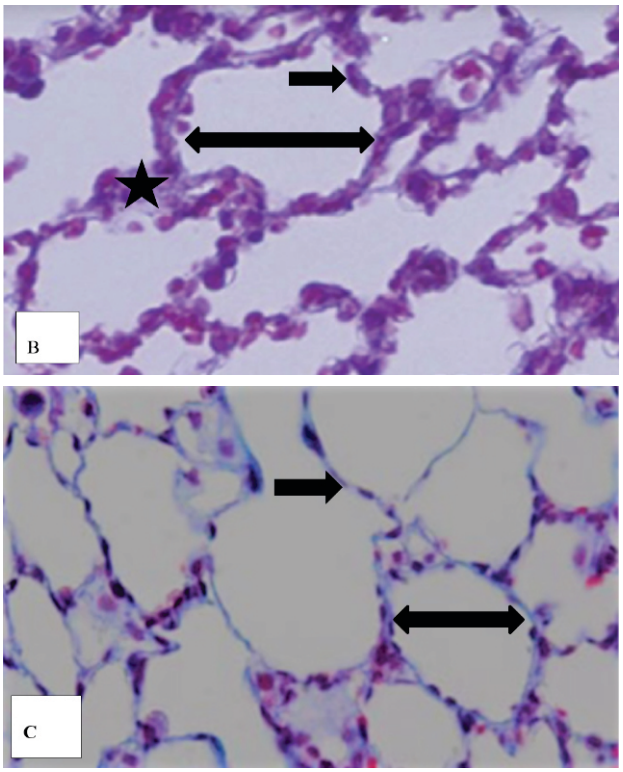


Fig 2: (A) Histological Section of a Rat Lung from Group M Showing Thickened Fibrotic Alveolar Septa (Arrow), Proteinaceous Fluid (Star) With Reduced Air Space (Double Headed Arrow)
(B) Histological Section of a Rat Lung from Group T Showing Less Thickened Alveolar Septa (Arrow) With A Few Cellular Infiltrates (Star), Well-Formed Alveoli and Preserved Air Space (Double Headed Arrow)
(C) Histological Section of A Rat Lung from Group X Showing Normal Alveolar Septa (Arrow) and Alveoli Showing Honeycomb Like Pattern (Double Headed Arrow)

Discussion

Pulmonary fibrosis is a pattern of reaction to parenchymal damage in which lung has unusually high collagen fiber content per unit volume of tissue.[14] In the present study histological sections of the lungs of rats are stained with Masson's Trichrome in order to observe the fibrotic thickening of alveolar septa, reduced air spaces and presence of proteinaceous fluid. 100% of rats in Group M showed thickened alveolar walls & proteinaceous fluid accumulated in interstitial space along with interstitial fibrosis. In Group T, only 28.5% of rats showed the said histopathological parameters. Inflammation is one of the etiological factor for the development of fibrosis.[14] As inflammatory reaction is observed in this case, it can be correlated to the development of fibrosis. Fibrosis in the pulmonary interstitium is usually a result of alveolar damage due to physical, chemical or microbial agents.[14] Allethrin in the coil smoke can be linked to the interstitial fibrosis observed in this study. The process of interstitial fibrosis is characterized by thickened alveolar walls that are fibrotic and contain an inflammatory cell infiltrate with reduced air spaces. Macrophages are thought to be responsible for expressing fibroblast growth factor, resulting in the proliferation of fibroblasts and subsequent development of fibrosis. The excessive deposition of collagen fibers reflects reduced lung capacity leading to respiratory distress which is the main effect of air pollutant exposure. Earlier study mentions that smoke induces lung destruction with inflammatory reaction, more fibroblasts are brought to the irritated area leading to more collagen fiber deposition.[15,16] In another study, fibrotic change was observed in lung parenchyma of rats after 6 weeks of exposure to mosquito coil smoke. Similar histological appearance was seen in the lungs exposed to asbestos and cigarette smoke.[17] Excessive deposition of collagen fiber has also been observed in the lungs of rats in similar inhalational studies.[18] Turmeric is one of the herbal compounds that has been investigated in fibrosis research.[19,20] In the present research only 28.5 % of histological sections of rat lungs in the Group T showed fibrous reaction. The result of this study is consistent with the previous studies. Turmeric administration can inhibit abnormal lung collagen formation.[21] Turmeric supplementation suppresses alveolar macrophages, expression of fibroblast growth factor by the macrophages and other inflammatory cells thereby ameliorating the inflammatory responses in the lungs which prevents fibrosis in the lung tissue.[22] The histopathological findings of the current research can further be utilized to test turmeric for the prophylaxis and treatment of Covid-19 induced pulmonary fibrosis; which is considered to be the most devastating outcome of this viral infection.[23]

Conclusion

Interstitial lung fibrosis caused by anti-mosquito coil smoke can be protected with the use of turmeric.

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ORIGINAL ARTICLE

Migration and Psychosis: Evidence from South Asian Communities in Bradford

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ABSTRACT

Objective: To study the risk of psychosis in south Asian communities in Bradford and investigate the role of cannabis as a contributory factor.

Study Design: Naturalistic studies based on electronic summary records.

Place and Duration of Study: The studies were conducted at the Becklin Centre, St James's University Hospital, Leeds and the University of Leeds, School of Medicine from 2018 to 2020.

Material and Method: A service evaluation and research project looking into the role of cannabis included 194 patients admitted to acute psychiatry wards at the Becklin Centre between 1st January 2016 and 30th November 2018. Epidemiological study used electronic summary records provided by the Bradford Early Intervention for Psychosis Service of 15-35-year old newly diagnosed cases with first episode psychosis in 2013-15 and local census data to calculate the risks ratios.

Results: Compared with indigenous white population, Pakistanis in Bradford had significantly higher risk of psychosis (RR: 1.41, 95% CI 1.07, 1.85*). This trend was also seen in Bangladeshi community (RR 1.72, 95% CI 0.91, 3.28*). Indian community, on the other hand, experienced lower risk (RR 0.54, 95% CI 0.20, 1.27).

Conclusion: We found increased risk of psychosis in Pakistani and Bangladeshi communities but not in Indian community.

Key Words: *Bradford, Ethnic, Psychosis, Risk Ratio.*

Introduction

The association between migrant status and schizophrenia was reported in 1930s among Norwegian immigrants in New York[1,2] which suggested that stressful life experiences played a role in the causation of psychosis. An influential paper, in which the Norwegian psychiatrist Odegaard[3] reported the findings of his study in Wisconsin, argued that the increased incidence could be attributed to selective migration of people who were genetically at a higher risk. This was handy munition for anti-immigration politicians of that time and although later studies did not support this claim[4] it stymied further investigations in the field. Interest in the topic was rekindled in the 1980s by findings concerning first and second generation African Caribbean in the UK. These studies found that the incidence of schizophrenia was 4-6 times higher than the indigenous white population and was more marked in the second generation.[5]

Whilst an increased incidence of schizophrenia has been consistently reported in people of African Caribbean origin who are resident in the UK, the results are less consistent for those of south Asian origin. In the ÆSOP[6] study, the incidence of psychosis, although increased, was raised to a much lesser extent in Asian and non-indigenous white populations. Another study in east London, had found the incidence to be raised in most migrant and minority ethnic groups, however, in Pakistani and Bangladeshi populations, this trend appeared to be evident only in women.[7]

Bradford (population 530,000), a Yorkshire city with a rich industrial history of cotton and woollen mills, is home to a number of immigrant communities from the subcontinent including Pakistanis, Bangladeshis and Indians. Pakistanis from Kashmir in the north of Pakistan are the largest ethnic group (110,000) and there are sizeable Indian and Bangladeshi populations.

Anecdotally, the prevalence of schizophrenia among Pakistanis in Bradford was said to be 2-5 times higher and since the district has the largest proportion

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(20.3%) of people of Pakistani origin in England, there was an opportunity to study these reports in a systematic manner.[8,9] This was made easier by the existence of an early intervention service (EIPS) in Bradford since 2005, which up until 2016 accepted cases in 15-35 age band and had gathered a substantial case load. According to unpublished EIPS data 29.5% of Bradford EIPS referrals were of Pakistani ethnicity.

Migrant status is now a well-recognised risk factor for the development of psychosis; however, its antecedents have not been that well elucidated. Social disadvantage, unemployment and residence in densely populated inner- city areas are applicable to new immigrants[10] however, it is the use of illicit substances which is often under the spotlight. There are reports to suggest that cannabis use has a greater effect in inducing psychosis in urban environments.[11] The evidence, however, is sketchy as there are no systematic studies of migrant populations such as community surveys, possibly due to the difficulty, which any attempt to gather such stigmatising information will encounter. We, therefore, addressed this question indirectly by looking into the drug use histories of patients (ICD-10, F20-29) of various ethnic backgrounds admitted to an acute psychiatry unit in Leeds, a neighbouring Yorkshire city (population 800,000) with sizeable populations of south Asian origin. The findings of this Extended Study Research Project (ESREP) undertaken by two University of Leeds 4th year medical students are reported in this paper.

Material and Methods

As reported in an earlier paper[8] by Saleem et al in 2019, EIPS Bradford provided anonymous summary data on the number of 15-35 year old newly diagnosed with first episode psychosis in 2013, 2014 and 2015, grouped by ethnicity, gender and 10-year age bands. Permission to use these data for the current study was granted by the Medical Director of Bradford District Care NHS Foundation Trust. EIPS Bradford uses comprehensive assessment of at risk mental state (CAARMS) interviews to establish the diagnoses according to ICD-10 criteria.[12] Only cases with non-affective first episode psychoses were included. The RevMan 5.3 program[13] was used for analysis and data from the three years 2013-15 were combined. Risk ratios (RRs) with 95% confidence intervals were calculated and RRs with 95% confidence intervals that did not include 1 were regarded as statistically significant at $p<0.05$, two-tailed.

Population data were obtained from 2011 census figures published on the website of the Office of National Statistics. Table I shows the basic demographic data derived from Census 2011, which provides the denominators for relative risk (RR) calculations. Compared with British white in Bradford (23% in 15-35 age band), the three south Asian communities are youthful, as 36 – 48% of their members fall in this age band. Another noteworthy observation is female preponderance in British white, Pakistani and Bangladeshi communities. Indian community, on the other hand, has fewer females.

Extended Study Research Project (ESREP) obtained the ethnicity and drug use data from the electronic records of 194 patients admitted with ICD10 (F20-29) diagnosis of psychosis to four acute adult wards at the Becklin Centre between 1st January 2016 and 30th November 2018. Fifteen patients were excluded as no data on cannabis use was available in their electronic case notes. Patients were categorised as either "white British" (n=101, male 72, female 29) or "non-white British" (n=78, male 52, female 26). Parametric and non-parametric tests were used to analyse the data. Research approval was granted by the Leeds & York Partnership Trust Research & Development and ESREP board of the University of Leeds, School of Medicine (R&D 2018-673-SE).

Table I: Census 2011 Data for Bradford†

Ethnicity	Total	15-24	25-35	Men (15-35 year)	Women (15-35 year)
White	333628	38961	38012	37953	39020
Pakistani	106614	18252	23125	20357	21020
Bangladeshi	9863	1744	2058	1751	2051
Indian	13555	1924	2902	2433	2393

†Adapted from Saleem et al [8]

Results

Table II shows the risk of first episode psychosis for each ethnic group. Compared with UK White population, Pakistanis, and Bangladeshis had higher

incidence rates (50, 71, 87/100000 respectively in 15-35 age band). People of Indian origin, on the other hand, had a lower incidence rate (27/100000).

Table II: Incidence of Psychosis and Risk Ratio

	Cases Accepted by EIPS	15-35 Age Band Incidence	Risk Ratio Relative to White†
Ethnic group	2013-2015	Cases/100000 per year	(Confidence Interval)
White	122	50.85	1.0
Pakistani	89	71.69	1.41(1.07-1.85)*
Bangladeshi	10	87.67	1.72(0.91-3.28)‡
Indian	4	27.62	0.54(0.20-1.27)

*Statistically significant at p<0.05 ‡ Trend towards significance †Adapted from Saleem et al [8]

Table III shows the risk of psychosis in 10-year age bands for each ethnic group. The risk compared to whites is significantly higher in 25-35 old Pakistanis (RR 1.92, 95% CI 1.29, 2.87) and Bangladeshis (RR 2.64, 95% CI 1.13, 6.19). In contrast to the British White, British-Indian population appears to show a lower risk for this age group.

Table III: Risk of Psychosis by Ethnic Group and 10-Year Age Bands

		Cases Accepted in	Incidence	Risk Ratio†
Ethnic Group		2013-2015	Cases/100000	(95% CI)
White	15-24	76	65.02	-
	25-35	46	36.74	-
Pakistani	15-24	40	73.05	1.12 (0.77,1.65)
	25-35	49	70.63	1.92 (1.29,2.87)*
Bangladeshi	15-24	4	76.45	1.18 (0.43,3.21)
	25-35	6	97.18	2.64 (1.13,6.19)*
Indian	15-24	3	51.79	0.80 (0.25,2.53)
	25-35	1	11.48	0.31 (0.04,2.27)

*statistically significant at p<0.05
†Adapted from Saleem et al [8]

Table IV Shows gender analysis of risk in the four ethnic groups. We see significantly increased risk for Pakistani and Bangladeshi males (RR 1.46, 95% CI 1.16, 1.83; 2.42, 95% CI 1.17, 5.02)) whereas Indian males showed a non-significant lower risk (RR 0.65, 95% CI 0.21, 2.07).

Table IV: Risk of Psychosis by Ethnic Group and Gender

Ethnic Group		Cases accepted	Incidence	Risk Ratio†
Gender		2013-2015	Cases/100000	(Confidence Interval}
White	Male	75	62.84	1.0
	Female	47	38.98	1.0
Pakistani	Male	66	108.07	1.72(1.24, 2.39)*
	Female	23	36.47	0.94(0.57, 1.54)
Bangladeshi	Male	8	152.29	2.42(1.17, 5.02)*
	Female	2	32.50	0.83(0.20, 3.43)
Indian	Male	3	41.10	0.65(0.21,2.07)
	Female	1	13.92	0.36(0.05, 2.59)

*statistically significant at p<0.05
†Adapted from Saleem et al [8]

The ESREP carried out by medical students CB and FR found a high rate (53.70%) of cannabis use in all acute patients admitted with a diagnosis of ICD-10 psychosis. Table V compares the rates of cannabis use in white British (47.52%) and non-white British (60.26%) patients and shows a trend towards greater use in non-white British (x^2 =2.864, p 0.091; OR 1.554, 95% CI 0.824,2.933).

Table V: History of Cannabis Use in Acute Psychiatric Admissions

Ethnicity	Cannabis user	Non-cannabis user
British White	48 (47.5%)	53(52.5%)
Non-British white	47(60.3%)‡	31(39.7%)

‡ p 0.091

Discussion

Higher Risk of Psychosis in Immigrant Communities

This naturalistic study confirmed the anecdotal reports of higher incidence of psychosis in Bradford South Asian ethnic groups and found that it is true in the case of British Pakistani and British Bangladeshi communities (RRs 1.41 and 1.72). However, the risk for British Indians is lower (RR 0.54), which is surprising but not unique as it has been reported before.[14] Stillman and McKenzie (2009) report the findings of a study of Tongans, who were selected through a ballot and accepted for migration to New Zealand. Compared with those who were unsuccessful in the ballot, the mental health of migrants, particularly women, was significantly

better. This study, however, was carried out only 11 months after resettlement in New Zealand and it will be interesting to see if the Tongans in New Zealand continue to enjoy the positive effect of migration, which Indian migrants in Bradford have experienced over 50 years.

Duration of Untreated Psychosis

This is a noteworthy finding that Pakistani and Bangladeshi group has a significantly higher risk in the age band 25-35 years, which suggests late presentation for treatment and is consistent with anecdotal reports that patients are first taken to traditional healers[15], a practice brought over from their homelands. This practice, unfortunately, prolongs the duration of untreated psychosis[16] which is well known to have an adverse effect on outcome.[17] It may, therefore, pay to promote mental health education amongst ethnic communities and their traditional healers.

Gender differential

In their east London study Coid et al[7] had found a small increase in the risk of psychosis in Pakistani and Bengali women. We found a higher risk of psychosis in Pakistani and Bengali men, which is more consistent with observations of local mental health practitioners and psychiatrists practising on the subcontinent.

Underlying factors

Schizophrenia is a serious and enduring illness which causes great suffering to affected individuals and their families and generates a huge societal burden. It is imperative, therefore, that we try to find the causes of increased risk of psychosis in ethnic populations. One factor which distinguishes Bradford Pakistanis from other populations is a high rate of first cousin marriages which is reported to be as high as 70% [18] and has increased from 55% found by Darr & Model[19] in 1988, which was an increase on 33% among the mothers of women included in that study. Dobrussin and colleagues[20] have shown that the risk of developing schizophrenia is elevated in populations with high consanguinity. Therefore, it may be that the higher incidence of schizophrenia among Bradford Pakistani and Bangladeshi communities is partly due to elevated genetic loading associated with cousin marriages.

Based on the observation that cannabis use can increase the risk of developing schizophrenia, Hickman et al[21] quantified the theoretical increase in the incidence and prevalence of schizophrenia that may follow a population wide increase in the use of cannabis. Their models predicted that by 2010, cannabis use will lead to 29% increase in incidence of schizophrenia among men. The ESREP project undertaken by Leeds University medical students CB and FR under the supervision of TM and AC addressed this question as to whether cannabis use is a modifiable risk factor for increased psychosis in ethnic populations. They found a trend towards greater cannabis use in non-white British patients, which suggests that a larger study such as a community survey is needed to find a definitive answer to this question.

The naturalistic design of these studies has some limitations such as reliance on electronic summary data precludes analysis of individual variations. However, this is offset by the fact that research on populations and themes, which tend not to attract the attention of grant giving bodies, can be carried out by workers such as enthusiastic medical students and junior doctors, who are prepared to give their time out of goodwill to the cause of science.

Conclusions

Compared with indigenous whites in Bradford, south Asians of Pakistani and Bangladeshi origin are experiencing a higher risk of psychosis, though, the incidence rates do not appear to be as elevated as in those of African and Caribbean origin. However, this does not completely disprove the anecdotal reports of increased prevalence among some ethnic groups which may be due to delayed recognition suggested by elevated incidence rates in 25-35 age band, thus increasing the duration of untreated psychosis and decreasing the chances of better outcome. In view of the above, it will not be out of place to make the customary call for more research to find the definitive answers. However, the fundamental questions such as genetics of schizophrenia may take more time to be answered or they may be un-answerable as they are integral to human condition. In the meantime there is cause for optimism in that some of the underlying factors such as cannabis use are modifiable with health education and adoption of preventive strategies.

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ORIGINAL ARTICLE

Antibacterial Susceptibility Pattern of Gram-Negative *ESKAPE* Pathogens Isolated From Hospitalized Patients

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ABSTRACT

Objective: To determine in-vitro antimicrobial susceptibility pattern of multidrug resistant (MDR) strains of Gram-negative *ESKAPE* pathogens using VITEK 2 Compact system.

Study Design: Descriptive Cross sectional study.

Place and Duration of Study: The study was conducted at Pakistan Railway hospital (PRH) Rawalpindi in collaboration with Armed Forces Institute of Pathology (AFIP) Rawalpindi from 1st September 2018 to 1st September 2019.

Material and Methods: A total of 320 clinical specimens were collected. The samples included urine, blood, pus, wound, effusions, C.S.F and sputum. After processing the isolates by standard microbiological methods, the antibiotic susceptibility pattern was carried out using VITEK 2 Compact system.

Results: A total of 190 clinical isolates of Gram-negative *ESKAPE* pathogens isolated from 320 clinical specimens. Among them 150 MDR Gram negative *ESKAPE* pathogens were detected. Out of 190 Gram-negative *ESKAPE* pathogens, (30.5%) were members of the family *Enterobacteriaceae* and (69.4%) were from *non Enterobacteriaceae.* The commonest isolated organism was *Acinetobacter baumannii*, 36% followed by *Pseudomonas aeruginosa*, 33.7%, *Klebsiella pneumoniae*, 26.3% and *Enterobacter spp.* 4.2%. From all isolates 88% of *Klebsiella pneumoniae*, 86.9% of *Acinetobacter baumannii* and 73.4% of *Pseudomonas aeruginosa* were found MDR.

Conclusion: Rapid identification and susceptibility testing of Gram-negative *ESKAPE* pathogens by VITEK-2 compact system helps in reducing total consumption of antibiotics. MDR was observed in majority of Gram-negative *ESKAPE* pathogens except for *Enterobacter spp*. These pathogens revealed comparatively better susceptibility against Minocycline, Tigecycline, and Colistin.

Key Words: *Colistin, Enterobacteriaceae, ESKAPE Pathogens, Multidrug-Resistance, Vitek 2 Compact System.*

Introduction

In the last decade along with the problem of Healthcare associated Infections (HCAIs), the prevalence of multidrug-resistant (MDR) organisms in hospitals has been greatly increased. The most frequently isolated six MDR bacterial species around the world have been grouped under the acronym *ESKAPE* in 2008 by Infectious Diseases society of America. It includes two Gram-positive cocci (*Enterococcus faecium* and *Staphylococcus aureus)* and four Gram-negative bacilli (*Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter spp*).[1] These superbugs are widely distributed and are frequently resistant to antibiotics.[2] They have the capability of 'ESCAPING' the biocidal action of antibiotic and communally representing new paradigms in transmission, pathogenesis, and resistance.[1] Today they are considered to be major threats and are responsible for two-thirds of all Healthcare-associated Infections (HCAIs) in both developed and developing world.[3] They lead to increase morbidity & mortality, due to severe and life-threatening infections, especially if the host is debilitated or immunosuppressed (e.g. AIDS, cancer and transplant patients, patients with autoimmune diseases, old age, neonates).[4] The World Health Organization selected anti-microbial resistance (AMR) as the theme for World Health Day 2011. Their slogan was "Combat Drug Resistance – No action

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today, no cure tomorrow." [4]

ESKAPE pathogens with built in abilities have a variety of mechanisms to find new ways to be resistant to multiple classes of current antibiotics. Gram-negative *ESKAPE* pathogens are particularly concerning because their multidrug-resistant phenotypes frequently present clinicians with few therapeutic choices.[5]The important mechanisms of antibiotic resistance are: Chromosomally-encoded enzymes such as Extended-spectrum beta-lactamase (ESBLs), Cephalosporinases (AmpC) and Carbapenemase. In addition decreased permeability through Porin channels loss due to mutations and activation of multi-drug efflux pumps.[6] Acquisition of plasmids and mobile genetic elements carrying multiple resistance genes also contributes to the development of multidrug-resistant phenotypes.

A recent study found 2,609,911 new patients with HCAIs annually in the European Economic Area and the European Union. *Acinetobacter* species and the *Klebsiella pneumoniae* were extremely resistant to multiple anti-microbials. The lack of new anti-biotics has mounted huge burden in European Union.[7]

In Southeast Asian countries a systematic review and meta-analysis regarding HCAIs found an overall prevalence rate of 9.1%. The most common micro-organisms being *A. baumannii, P. aeruginosa,* and the *Klebsiella species*.[8]

In order to keep regular monitoring of MDR at species level the changing trends in the susceptibility patterns of Gram-negative *ESKAPE* pathogens should be known. It is essential for detection or at least controlling the outbreaks, identifying the population most at risk, designing and evaluating intervention strategies. This study was therefore, planned to know the susceptibility pattern of all the Gram negative *ESKAPE* pathogens isolated at our set up.

Material and Methods

It was a descriptive cross-sectional study, conducted at PRH Rawalpindi in collaboration with AFIP Rawalpindi, after getting formal approval from Institutional Ethical Review Committee. All the samples coming to Microbiology labs for culture and sensitivity report were processed. Gram negative *ESKAPE* pathogens (*Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* & *Enterobacter species*) recovered from these clinical specimens were included in our study. Duplicate samples were excluded from the study. A demographic proforma specially designed for this purpose was filled to avoid duplication of samples.

Three hundred and twenty samples from different sources like urine, blood, pus, wound, throat infection, nose infection, effusions, C.S.F and sputum were collected from hospitalized patients. The samples were inoculated on suitable culture media depending upon the type of specimen. CLED agar was used for inoculation of urine specimens. Blood agar and MacConkey agar were taken for all other specimens. The culture plates were incubated aerobically at 37°C for 24 hours & re-incubated for next 24 hours if growth was not sufficient. After incubation, bacterial isolates were identified by performing Gram staining and standard biochemical tests which included catalase test, oxidase test, and Analytical profile index (API).

Sub-culture of mixed colonies for GNR was done on MacConkey agar to obtain a pure culture. *Escherichia coli* ATCC 25922 was used for quality control. A total of 320 samples were collected from different clinical samples. Culture positive samples (n=190) were included in the study. These isolates were stored in glycerol broth, as MICs was runs in batches by using Vitek-2 Compact system (bioMérieux). Preserved specimens were thawed at room temperature then subculture on MacConkey agar and incubated for 24-48 hours at 37°C. Antimicrobial Susceptibility tests were performed with AST-N222 cards which contained the dehydrated form of the following antimicrobial agents.

Amikacin, Ticarcillin, Ticarcillin- Clavalanic acid, Piperacillin, Tazobactam-Piperacillin , Ceftazidime, Ciprofloxacin, Imipenem, Levofloxacin, Minocycline, Tobramycin, Trimethoprim-Sulfamethoxazole, Gentamicin, Meropenem, & Colistin. The susceptibility breakpoints were those recommended by CLSI.

Data analysis was done by using SPSS 21. For qualitative variables (gender of patient, type of samples and organisms isolated), percentages and frequencies were calculated. Descriptive numerical (continuous) variables of age (years) was calculated in terms of Mean ± SD (standard deviation).

Results

Three hundred and twenty different samples obtained from hospitalized patient were processed.

One hundred and ninety (59.3%) Gram-negative *ESKAPE* isolates were included in the study. The pathogens belonging to family *Enterobacteriaceae* (*Klebsiella pneumoniae* & *Enterobacter species*) were 58(30.5%) and *non Enterobacteriaceae* (*Acinetobacter baumannii* & *Pseudomonas aeruginosa*) were 132(69.4%). *Acinetobacter baumannii* 68(36%) was the commonest isolate, followed by *Pseudomonas aeruginosa* 64(33.7%), *Klebsiella pneumoniae* 50(26.3%) and *Enterobacter spp*. 8(4.2%).

They were mostly recovered from Medical Intensive Care Unit patients' specimens, followed by Surgical Intensive Care Unit, and Pulmonology ward. Isolates were mostly yielded from pus, followed by blood, and urine specimens. The distribution of Gram-negative *ESKAPE* pathogens recovered from different specimens is presented in table I.

Out of the total isolates, 54.7% were recovered from male patients and 45.3% from female patients. Mean age of the patients was 47.19 years ± 19.91 SD. Majority 44 (23%) of the subjects had ages between 40-49 years.

Among all 190 isolates, 150 were found to be MDR (88% of *Klebsiella pneumoniae*, 86.9% of *Acinetobacter baumannii* and 73.4% of *Pseudomonas aeruginosa*). There were only 8 isolates of *Enterobacter spp*. Which were found sensitive to most of antibiotics, we excluded them from final analysis.

Antibiotic Sensitivity Testing by Vitek-2 Compact system showed that the resistance frequency of *Acinetobacter baumannii* against Ticarcillin, Ticarcillin-Clavulanate and Tazobactam-Piperacillin was 96.6%. Highest resistance was observed in case of Ciprofloxacin (100%). Colistin was again the most successful antibiotic.

The resistance frequency of *Klebsiella pneumoniae* against Ticarcillin and Piperacillin was 100% with a maximum MIC of ≥128 µg/ml and Cefipime and Ceftazidime with an MIC of ≥ 64 µg/ml. The resistance frequency of *Pseudomonas aeruginosa* against Ticarcillin and Tazobactam-Piperacillin was 95.7% with a maximum range of ≥ 128 µg/ml. Colistin was effective against (62%) of the total isolates of *Pseudomonas aeruginosa* tested.

None of the isolates was 100% susceptible to all of the tested anti-microbials. Furthermore, 25.4% (15/59) of *A. baumannii* and 27.2% (12/44) of *K. pneumoniae* isolates were found to be Extensively Drug Resistant because they showed resistance to all antimicrobial agents evaluated.

The antibacterial susceptibility pattern of MDR strains of *non-Enterobacteriaceae* is displayed in table II and antibacterial susceptibility pattern of MDR strains of *K. pneumoniae* is shown in Table III.

Table I: Distribution of Gram-Negative *ESKAPE* Pathogens Recovered From Different Specimens

Specimens	*Klebsiella pneumoniae*	*Acinetobacter baumannii*	*Pseudomonas aeruginosa*	*Enterobacter Spp.*
	n (%)			
Pus	11(22)	21(30.9)	22(34.4)	3(37.5)
Urine	10(20)	10(14.7)	17(26.6)	5(62.5)
Blood	6(12)	17(25)	8(12.5)	-
Catheter Tip	3(6)	2(2.9)	4(6.3)	-
Tissue	6(12)	3(4.4)	2(3.1)	-
CSF	-	9(13)	1(1.6)	-
Sputum	3(6)	-	5(7.8)	-
EB washing	11(22)	6(8.8)	5(7.8)	-

Table II: Antibacterial Susceptibility Pattern of MDR Strains of *Non-Enterobacteriaceae* by Vitek- 2 Compact System

Antibiotics	*A. baumannii* (n=59)			*P. aeruginosa*(n=47)		
	S (%)	I (%)	R (%)	S (%)	I (%)	R (%)
Ticarcillin	2(3.4)	-	57(96.6)	2(4.2)	-	45(95.7)
Ticarcillin/ Clavulanic acid	1(1.7)	2(3.4)	56(94.9)	3(6.3)	1(2.1)	43(91.5)
Pipracillin	1(1.7)	1(1.7)	57(96.6)	3(6.3)	1(2.1)	43(91.5)
Tazobactam/ Piperacillin	2(3.4)	-	57(96.6)	2(4.2)	-	45(95.7)
Ceftazidime	1(1.7)	1(1.7)	57(96.6)	4(8.5)	-	43(91.4)
Cefipime	3(5)	3(5)	53(89.8)	3(6.3)	1(2.1)	43(91.4)
Imipenem	23(38.9)	-	36(61)	7(14)	-	40(85.1)
Meropenem	5(8.4)	5(8.4)	49(83)	9(19.1)	-	38(80.9)
Gentamycin	6(10.1)	6(10.1)	47(79.6)	15(31.9)	-	32(68.1)
Tobramycin	14(23.7)	3(5.1)	42(71.1)	6(12.8)	4(8.5)	37(78.7)
Ciprofloxacin	2(3.3)	-	57(96.6)	5(10.6)	-	42(89.4)
Minocycline	27(45.7)	-	32(54.2)	29(59.1)	-	20(40.8)
Trimethoprim/ Sulfamethoxazole	19(32.2%)	-	40(67.9)	35(74.4)	-	12(25.5)
Colistin	37(62.7)	-	22(37.2)			

R: Resistance I: Intermediate S: Sensitive

Table III: Antibacterial Susceptibility Pattern of MDR Strains of *K. Pneumoniae* by Vitek- 2 Compact System

Antibiotics	*Klebsiella pneumoniae* (n=44)		
	S (%)	I (%)	R (%)
Ticarcillin	-	-	44(100)
Ticarcillin/Clavulanic acid	-	2(4.5)	39(95.1)
Pipracillin	-	-	41(93.1)
Tazobactam/Piperacillin	2(4.5)	-	42(95.5)
Ceftazidime	-	4(9.1)	40(90.9)
Cefipime	1(2.3)	1(2.3)	42(95.5)
Imipenem	7(15.9)	2(4.5)	35(79.5)
Meropenem	6(13.6)	-	38(86.4)
Gentamycin	4(9.1)	3(6.8)	37(84.1)
Tobramycin	4(9.1)	2(4.5)	38(86.4)
Ciprofloxacin	-	-	44(100)
Minocycline	24(54.5)		28(45.5)
Trimethoprim/Sulfamethoxazole	10(25)	-	30(75)
Colistin	28(68.2)	-	13(31.7)

R: Resistance I: Intermediate S: Sensitive

Discussion

It is worrisome to note the high rates of resistance of *non Enterobacteriaceae* members of gram negative *ESKAPE* pathogens i.e. *Acinetobacter baumannii* and *Pseudomonas aeruginosa* to the commonly used flouroquinolone (ciprofloxacin) in our study i.e. 77.9 % and 81.3% respectively, while *Klebsiella pneumoniae* showed 58% resistance and *Enterobacter spp*. 100% sensitivity to ciprofloxacin.

In present study MDR *Acinetobacter baumannii*, was the most common pathogen recovered from clinical specimens (36 %). Similar findings have been reported in another study conducted in an Intensive Care Unit of Monterrey, Mexico, in which *Acinetobacter baumannii*, was also found to be the most common isolate.[2]

Multidrug resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* are now emerged as one of the very important healthcare-associated infections to control and treat. Patients admitted in intensive care unit (ICU) and those with central intravenous catheters and respiratory devices are the main targets of these organism.[9]

MDR *Acinetobacter baumannii* demonstrated high rate of resistance to Ciprofloxacin 38% Piperacillin,78% & Ceftazidime 45% in the previous studies by Bruno et al., and Simgamsetty et al.,[10] which were contradictory to the results found in our study, that is resistance to Ciprofloxacin was 96.4%, to Ceftazidime 96.6% and to Piperacillin 96.6%. Viaggi et al., reported 96% *Klebsiella pneumoniae* isolates resistant to Meropenem (MIC>16 mg/L) while (92%) were resistant to Tigecycline (MIC >1 mg/L), Colistin (MIC >2 mg/L), and Gentamicin (MIC >2 mg/L).[11] Our result showed only 31.7% resistance of *Klebsiella pneumoniae* to Colistin (MIC >16), 84.1% to Gentamicin and 86.4% to Meropenem having MIC of >16.

Colistin is considered as one of the therapeutic option against isolates of *Acinetobacter baumannii* and *Klebsiella pneumoniae*.[12] *Pseudomonas aeruginosa* MDR isolates in our study showed > 90% resistance to Ticarcillin, Meropenem, Cefipime, Ceftazidime and Piperacillin, while 74.5% sensitivity to Cotrimoxazole, but contradictory findings were observed by Shashwati et al.,[13] and Ibrahim of Thi-Qar university.[14] They reported that majority of *Pseudomonas aeruginosa* isolates were susceptible to Cefepime, Cefoperazone-Sulbactum, Meropenem, Levofloxacin, & Amikacin. A study conducted by Ghazal et al., demonstrated 93.7% of *Pseudomonas aeruginosa* resistant against Ceftazidime, 72% against Ciprofloxacin and 52% against Amikacin.[15] It is comparable with our study which revealed almost similar susceptibility pattern.

The study being laboratory based is the limitation of this research. No clinical outcome of antibiotic therapy was determined. A multicenter study should be carried out involving all main hospitals of the city to establish MDR pattern in Gram-negative *ESKAPE* pathogens. However, this study will help doctors in our locale while deciding antimicrobial options for treating infectious diseases.

Conclusion

It is concluded that rapid identification and susceptibility testing of Gram-negative *ESKAPE* pathogens by VITEK-2 compact system helps in earlier switches in antibiotic therapy, and reducing total consumption of antibiotics. Moreover**,** MDR was observed in majority of Gram-negative *ESKAPE* pathogens except for *Enterobacter spp*. in our setup. Most of Gram-negative *ESKAPE* isolates were found to be susceptible against Colistin, Tigecycline and Minocycline. These antibiotics could be the good therapeutic options for infections due to *ESKAPE* pathogens. However, it is recommended that Colistin has to be used cautiously due to more significant adverse effects like neurotoxicity and nephrotoxicity and should be kept for use for more resistant Gram negative *ESKAPE* pathogens.

Future Prospects

The anticipated regional variations of MDR, requires consistent checking of disease control processes and ordinary surveillance of antimicrobials susceptibility profile in our hospitals. It should be the joint effort of microbiologists and clinical practitioners in introducing current and suitable antimicrobials according to AMR trend and locally designed antibiogram.

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ORIGINAL ARTICLE

Effect of Modified Constraint Induced Movement Therapy on Improving Hand Function of Stroke Patients

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ABSTRACT

Objective: The current study was aimed to assess the role of Modified constraint induced movement therapy (mCIMT) on hand function of hemiplegic patients.

Study Design: An experimental randomized control trial.

Place and Duration of Study: The study was conducted in Rural Health Care Hospital and Almeraj clinic, Nankana sahib from 1st may 2019 to 29th September 2019.

Material and Methods: Total 30 patients were recruited through non probability convenient sampling. Experimental group (15 subjects) received mCIMT and conventional therapy, while control group received only conventional treatment for 2 weeks. Fugl Meyer assessment scale and Motor assessment scale were used for assessment of treatment and control groups. Paired sample T-test was used for the comparison of before and after results of treatment and control groups. Mann-Whitney U test was used further to compare treatment and control groups independently.

Results: In upper arm function, the mean rank of control group and treatment groups were 9.37 and 21.63. The mean ranks of hand movements in control and treatment groups were 8.97 and 22.03 respectively. Advanced hand activities had mean rank of 10.07 and 20.93 in control and treatment groups respectively. Motor function had mean ranks of 9.07 and 21.93 in control and treatment groups respectively. Here the p value of Mann-Whitney U test is 0.00 which is less than 0.05, this shows that the test is highly significant.

Conclusion: It is concluded that modified constraint induced movement therapy has presented improved upper arm function, hand movements, advanced hand activities and motor function.

Key Words: *Fugl Meyer Assessment Scale, Hemiplegia, Modified Constraint Induced Movement Therapy.*

Introduction

Constraint means “to limit” induced means “leading to do something” thus constraint induced movement therapy means to restrict the one normal limb with a mitt or glove and use the other affected limb for activities. This technique is more beneficial in patients of cerebrovascular accident.[1]

There are different methods used for CIMT and different treatment timings which affect the results of the study, which includes modified constraint induced movement therapy (mCIMT), massed practice and Forced Use. In all these methods, the unaffected extremity is limited with a mitt and the abnormal limb received below three hours of treatment each day, below four hours per day for two weeks and no treatment to the abnormal extremity respectively. The affected limb performs tasks like lifting, throwing, holding objects, buttoning and catching. These approaches lead to improvements in motor activity and ADLs.[2,3]

Modified constraint induced movement therapy (mCIMT) does not follow the same protocol as CIMT but has other sets of exercises after limiting the working hand with a splint and series of task oriented movements were performed with the weaker arm. It is not performed for 6 hours and patients don't need to wear splint for 90% of waking hours. Modified constraint induced movement therapy (mCIMT) considered to be best task specific approach for improving hand function, range of motion, quality of life, amount of improvement and advanced hand activities when measured with motor assessment scale, motor activity log and Fugl Meyer assessment scale as opposed to CIMT.[4]

Constraint induced movement therapy is based on two approaches: one is limiting the normal limb and

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second one is forceful practice of the abnormal extremity. This approach leads to permanent improved behavior of the abnormal extremity. This technique was developed after experimenting on monkeys, constraining the monkey's normal upper limb with the glove for days. Monkeys were able to use the affected limb for feeding and then they were able to achieve some of the functions with abnormal extremity. In the past, the affected limbs were not used and all the activities were performed by the healthy extremity which makes the affected limb even more prone to permanent disability.[5] More than 24% of subjects having upper limb dysfunction, due to CVA, can get better by constraining the normal limb and utilizing the damaged extremity with different tasks. Modified constraint induced movement therapy has different results than constraint induced movement therapy that needs to be learned.[6]

Stroke is the major problem which causes functional disability in adults. Nine out of ten people described 75% permanent disability due to hemiplegia that leads to dependent living. Increasing number (300\130000) of stroke cases in Pakistan focused on great need of therapeutic rehabilitation of hemiplegic hands to improve their fine motor skills. Modified constraint induced movement therapy (mCIMT) is a newer therapy technique and has prospective of enhancement of function.[7]

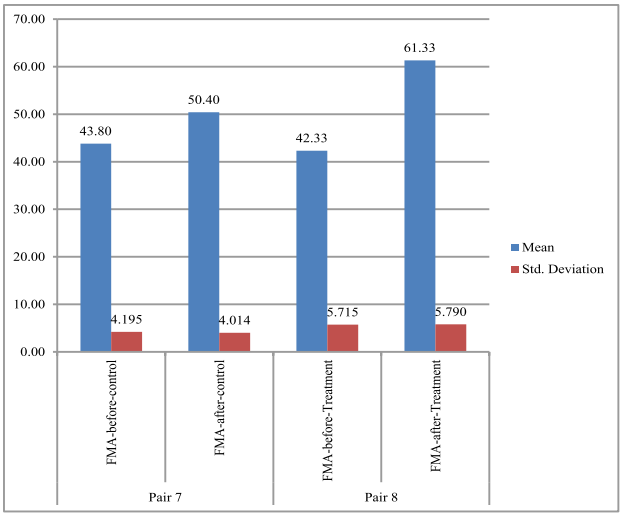
The objective of this study was to assess the role of Modified constraint induced movement therapy (mCIMT) on hand function of hemiplegic patients.

Material and Methods

This experimental randomized controlled study was conducted on hemiplegic patients (3 to 8 months) in Rural Health Care hospital and Almeraj clinic, Nankana sahib from may 2019 to September 2019. Total 30 patients recruited through non probability convenient sampling, aged between 40 to 60 years having minor spasticity of upper limb, able to extend wrist about 20 degree and interphalangeal joints about 10 degree were included for data collection. While those having pain (more than 4 on VAS), previous hand trauma and any psychological condition were excluded from the study. The subjects were enrolled after taking an informed consent for willingness to include in the study. 30 subjects (15 in each group) were divided in to two groups by lottery method; experimental group was treated by modified constraint induced movement therapy (mCIMT) and by conventional therapy while control group was treated by only conventional therapy (Pnf techniques, grasp release and range of motion exercises) for 2 weeks. In the experimental group modified CIMT was done by limiting the normal hand with glove and series of functional tasks were performed with affected hand. Non parametric Data was collected by using Motor Assessment Scale (upper arm function, hand movements and advanced hand activities) and Fugl Meyer assessment scale (motor function) before and after the treatment, paired sample T-test was used to check pre and post effects in control and treatment groups and Mann-Whitney U test was used to measure the difference between treatment and control groups. The results were then evaluated by SPSS (v. 20).

Results

Thirty subjects were treated through Modified CIMT (treatment group) and conventional therapy (control group) after division into two groups. The mean and standard deviation values of pre control group are 43.80± 4.195, while 50.40± 4.014 is the mean and S D of post control group treated by only conventional therapy. 42.33± 5.715 is the mean and standard deviations of pretreatment group while 61.33± 5.790 is the mean and standard deviations of post treatment group which is highest mean and standard deviations than all the other values. This depicts that



*Frequency distribution of Fugl Meyer assessment scale.

Fig 1: Frequency Distribution of Motor Function in Control and Treatment Group (N= 30)

mCIMT (treatment) group showed better results as the mean and standard deviation of mCIMT group after application of therapy is 61.33± 5.790 which is higher than conventional group (50.40± 4.014).

Table I: Frequency Distribution Between Control (Pre and Post) and Treatment Group (Pre and Post) (N= 30)

Motor Assessment Scale	Control Group(Conventional Therapy)			Treatment Group(Mcimt)		
Upper arm function	Pre Mean ±S.D	Post Mean ±S.D	P value	Pre Mean± S.D	Post Mean± S.D	P value
	2.47±1.187	4.20±1.146	0.000	3.20±1.082	5.80±0.561	0.000
Hand movements	1.40±0.737	2.87±0.834	0.000	1.93±0.799	4.80±0.862	0.000
Advanced hand activities	1.00±0.000	1.93±0.961	0.002	1.00±0.000	3.47±0.990	0.000

*Paired sample T-test comparing pre and post values of treatment and control groups.

*S D = standard deviation.

Paired sample T-test collectively shows the level of improvements in the results of patients who were treated with modified CIMT in treatment group. Firstly Upper arm function in post conventional group showed mean and standard deviation of 4.20± 1.146 which is less than post treatment group (5.80± 0.561). Secondly hand movements improved with mean of 2.87 and standard deviation 0.834 in post control group which is less than the mean and standard deviation of post mCIMT group (4.80± 0.862), Thirdly advanced hand activities are more advanced form of activities in motor assessment scale and its values are higher in post treatment group which is 3.47± 0.990 and post conventional group have values of 1.93± 0.961, which is less than post treatment values.

Here the p value for both groups is 0.000, which is less than 0.05.There is statistically significant difference exist between motor assessments scales of post control and post treatment groups.

After comparing pre and post treatment and pre and post control groups. Now compare the difference between treatment and control groups. In Upper arm function the mean rank of control group is 9.37, while in treatment group it is 21.63 which is higher than control group. The mean ranks of Hand movements; in control and treatment group are 8.97 and 22.03 respectively. Advanced hand activities have mean rank of 10.07 and 20.93 in control and treatment group respectively. In the control and treatment group motor function have values of 9.07 and 21.93 respectively. Control group showed less values of mean ranks than treatment group, which shows that there is increase in upper arm function, hand movements, advanced hand activities and motor function in treatment group. Here the p value of Mann-Whitney U test is 0.00 which is less than 0.05, this shows that the test is highly significant.

Table II: Comparison between Treatment and Control Groups (N= 30)

	Group 1	N	Mean Rank	Sum of Ranks
UAF Control and Treatment	Control	15	9.37	140.50
	Treatment	15	21.63	324.50
	Total	30		
HM Control and Treatment	Control	15	8.97	134.50
	Treatment	15	22.03	330.50
	Total	30		
AHA Control and Treatment	Control	15	10.07	151.00
	Treatment	15	20.93	314.00
	Total	30		
MF Control and Treatment	Control	15	9.07	136.00
	Treatment	15	21.93	329.00
	Total	30		

UAF = Upper arm function

HM = Hand movements

AHA = Advanced hand activities

Table III: Mann-Whitney U Test Comparing Treatment and Control Groups (N= 30)

	UAF control and treatment	HM control and treatment	AHA control and treatment	MF control and treatment
Mann-Whitney U	20.500	14.500	31.000	16.000
Wilcoxon W	140.500	134.500	151.000	136.000
Z	-4.069	-4.165	-3.486	-4.066
Asymp. Sig. (2-tailed)	.000	.000	.000	.000

*Mann-Whitney U test used for comparison between independent groups.

*p < 0.05 was taken as level of significance.

UAF = Upper arm function

HM = Hand movements

AHA = Advanced hand activities

Discussion

Modified constraint induced movement therapy when used with conventional therapy shows better results in performing complex hand movements and functional tasks than other treatment options like pnf techniques, grasp release exercises combined with range of motion. There were improvements in upper arm function, hand movements, advanced hand activities and motor function in the affected

hand and fewer improvements in control group. In Upper arm function the mean rank of control group and treatment groups were 9.37 and 21.63, which was higher than control group. In the same manner, the mean rank of Hand movements; in control and treatment group were 8.97 and 22.03 respectively. Advanced hand activities have mean rank of 10.07 and 20.93 in control and treatment group respectively. Motor function had values of 9.07 and 21.93 in control and treatment groups respectively. Control group showed less value of mean ranks than treatment group. Here the p value of Mann- Whitney U test is 0.00 which is less than 0.05, this shows that the test is highly significant. The results of the study are same as suggested by Taub, et al.[8] that upper arm function, hand movements and advanced activities are improved; when normal hand is immobilized with a mitt and series of tasks are being performed by affected hand with conventional therapy. Collecting the beans, holding objects and placing them to the desired point have been made easy by 2 weeks exercise session and following follow up. Our results are also supported by Priyanka and Bijayeta.[9] they conducted a randomized controlled trial on hemiplegic patients of sub-acute stage. 20 subjects have been treated by modified constraint induced movement therapy mCIMT (normal hand was covered by a glove) for 2 hours and control group has been treated by conventional therapy for 2 hours. Motor function and daily functional activities got better in affected hand through mCIMT. Fugl-Meyer assessment (FMA) explained the mean and standard deviation increased in treatment group (77.11± 2.22) than control group. While on the contrary, Hartman, et al.[10] compared the effects of constraint induced movement therapy with mirror therapy on upper extremity dysfunction due to cerebrovascular accident in sub-acute and chronic stage. Visual feedback has been given through mirror therapy and leads to illusion of both arms function normally. While there has been fewer improvements in other group treated by CIMT and conventional treatment as there is no visual feedback and upper limb remained in previous state of immobility with minor changes. The patients who received CIMT with mirror therapy have been improved (P value 0.0001) while others showed minor improvements in stroke patients.

Similar results were reported by other researcher that CIMT alone showed better results when compared with conventional therapy for one month. It has better outcomes in improving daily task specific activities even in chronic stage of learned non- use of the immobile limb.[11] The same results have been explained by Sirtori, et al.[12] in a systemic review that when comparison occur among CIMT, modified constraint induced movement therapy, forced used phenomenon and conservative therapy or no treatment. There is improvement in those patients treated by modified constraint induced therapy as those patients were wearing mitt for not more than 2 hours and there was no specific two hour training which make them tired and stressed. There is significant increase in the mean and standard deviations (61.44± 2.33) of mCIMT group. In the same way, a meta-analysis has been conducted by Coleman, et al.[13] the goal of the study is to find out the importance of modified constraint induced movement therapy (mCIMT) in ischemic stroke survivors when comparing with traditional therapy. Evaluation of data has been done by Fugl Meyer assessment scale, motor activity log, action research arm test and Wolf motor function test, to measure how well, how much quality of hand and wrist movement improved. The results of the study are supporting that mCIMT is much better technique with mean and standard deviation of 20.77± 1.00 which is higher than control group (18.99± 1.22).

A randomized control trial was conducted on acute post CVA patients to check the effectiveness of constraint induced movement therapy. Fugl Meyer assessment scale was used before and after the treatment session on 30 patients for 2 weeks, which showed improved behavior of patients treated by CIMT as TMS showed parts of improvement in cerebral hemisphere.[14,15] But a single blinded study was conducted by Dromerick, et al.[16] on 40 stroke patients. They performed exercise sessions in hospital for 4 weeks and outcomes were different, which explained that the abnormal hand function improved in flexion but no increase in extension and functi0onal activities improved in other group.

Due to limited time duration, small sample size was selected to check the effects of modified constraint induced movement therapy (mCIMT) in stroke survivors. Further only single upper limb was

selected; there was no inclusion of quadriplegic patients. This study included only hemiplegic patients who had stroke in 3 to 8 months and age between 40 to 60 years, while stroke effects on younger population also who is below 35. Further there was no follow up assessments (feedback) were followed in this study which shows for how long improvements persists after quitting exercise. There were less coordinated movements present in hand due to stroke, which need more weight bearing and core stability exercises.

Recommendations

This study can help in further studies on mCIMT. Upcoming authors can also compare the effects of mCIMT with other exercise therapies to find out the best possible treatment for stroke. Further younger population can also affected by stroke which can be included in future studies. Only single upper limb was selected in hemiplegic patients, while studies can be performed on quadriplegic patients. We selected only small sample size of hemiplegic patients who had stroke in 3 to 8 months; studies can be performed on large sample size in acute or chronic stroke patients and other than stroke.

Conclusion

It is concluded that modified constraint induced movement therapy provides improved upper arm function, hand movements, advanced hand activities and motor function than conventional therapy for the patients with hemiplegic stroke.

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ORIGINAL ARTICLE

Hepato-Protective Effects of Silymarin and Coffee in Rats

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ABSTRACT

Objective: To compare the effects of silymarin and coffee on liver enzymes in acetaminophen-induced hepatotoxicity in rats.

Study Design: Experimental-randomized control study.

Place and Duration of Study: The research was conducted from October 2018 to October 2019 in Pharmacology Department at IIMCT in mutual collaboration with National Institute of Health (NIH) Islamabad.

Material and Methods: At day 0 after initial blood sampling, Acetaminophen (300 mg/kg) by intraperitoneal route was given to 30 rats to induce hepatotoxicity. These rats were further divided into three experimental groups on day 8. Group 2 was a disease control group, Silymarin (100mg/kg) was given to group 3 rats and group 4 rats were treated with Coffee (200 mg/kg) through intragastric gavage for fourteen days. Terminal blood sampling was done at day 21 through cardiac puncture for biochemical estimation on same day. Mean± SEM was calculated and analyzed through SPSS 20. P value less than 0.05 was considered statistically significant.

Results: Our results showed major elevation ($p<0.05$) in alanine aminotransferase and aspartate aminotransferase levels in group 2 when compared to normal control -group. The rats treated with silymarin & coffee considerably ($p <0.05$) lowered biomarker enzymes in comparison to disease control group 2 respectively.

Conclusion: Coffee lowers ALT and AST levels as compared to Silymarin in Acetaminophen induced hepatotoxicity in rats.

Key Words: *Acetaminophen, Alanine Transaminase, Aspartate Aminotransferases, Coffee, Silymarin.*

Introduction

Liver injury has a diffused pathology and if not controlled effectively then may lead to fibrosis, cirrhosis and hepatocellular carcinoma.[1,2] There is high prevalence of all sorts of hepatitis in Pakistan. Also, Pakistan has been named as "Cirrhotic state" because both HBV and HCV are responsible for more than 75% of cirrhosis which further leads to hepatocellular carcinoma.[3,4] These all challenging diseases with high prevalence around the globe have less effective long term treatment which make them financial burden and cause of death.[2] Steroids, vaccines, interferons, antiviral drugs and many other conventional drugs, which are usually used for treating liver ailments, when administered chronically or sub-chronically have been found to have adverse effects.[5,6] Therefore in recent years exploration of antioxidants of plant source and their hepatoprotective potential is being under solemn consideration. So that people may consume them because the use of natural medication and nutritional habits is appreciated by general public usually.[7] Flavonoids are considered good antioxidant compounds generally due to their phenolic structures and inhibition of free radical mediated processes.[8] One of the flavonolignane extracted from milk thistle, "Silymarin" has been utilized for the treatment of various liver disorders that portray functional impairment or degenerative necrosis. It is familiar for its antioxidant, anti-inflammatory and anti-fibrotic properties and exhibits protective effects in different liver issues. It acts as a free radical scavenger which consequently prevents lipid peroxidation and its related cell injury by stabilizing the membrane.[9] Among the most commonly consumed beverages worldwide prepared from plants, coffee holds a significant position specifically among working people. It is the 2nd most traded commodity in the world having lots of diversities in

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types and ways of preparation from seeds. Over the last period of years immediate development has been seen in the Pakistan's beverage industry. There is growing market and prompt opening of different coffee shops for the people to approach it easily.[10] Coffee is not only an aromatic flavored drink but is also a rich source of dietary antioxidants.[7] It is a multiplex mixture of varying compounds including caffeine (1, 3, 7trimethylxanthine) and up to 1000 described phytochemicals which help in combating reactive oxygen species.[11] Epidemiological data over the last years shows the inverse relationship of coffee and the risk of several liver diseases.[7] Large amount of chlorogenic acid present in Coffee reduce the risk of glucose intolerance and Non-alcoholic fatty liver disease.[12] Redox equilibrium is restored as well as expression of pro-inflammatory cytokines is reduced. Specifically nicotinic acid present in Coffee is a potent anti-fibrotic agent while caffeine blocks TGF-b as well as suppression of DNA synthesis and enhances apoptosis of hepatic stellate cell (HSC). All these processes account for hepatoprotection. Thus it is proposed that two or more cups of coffee in a day protects the liver and ameliorates almost all liver ailments.[7,13,14,15]

So the present study was performed to compare the efficacy between Silymarin and Coffee in terms of reversal of hepatic damage.

Material and Methods

This randomized-control trial done by balloting method was conducted at the Pharmacology department with Multidisciplinary -Research -Lab at IIMCT in mutual collaboration of Animal -House in NIH, Islamabad from ctober 2018-Oct 2019. Accredited Ethical Review Committee of the institute approved the research proposal before starting the study. Research Grade Acetaminophen and Silymarin were obtained from Sigma Aldrich. Coffee beans were procured from Al-Fatah super store in Centaurus mall, Islamabad and sent to herbarium section of National Agriculture Research Centre (NARC) for identification and validation through proper taxonomic rules. Coffee beans were then grinded, powdered and kept airtight in cool and dry place. The present study included forty adult healthy male albino rats weighing 300-350 grams with normal baseline liver function tests. Exclusion criteria was female rats and abnormal liver function tests**.** Rats were kept under controlled environment with temperature of 20-25 degree Celsius and constant twelve hour dark and light cycle. No mortality or morbidity was observed during the whole period of experiment. Division was done into four groups having ten rats in each cage. Blood samples were drawn from two rats of every group at day 0 by intracardiac blood sampling method. Group 1 was a control group which received normal diet and tap water. Rats in other three groups were given Acetaminophen 300 mg/kg injection through intraperitoneal route (just once at day 0) for the induction of hepatotoxicity. To assess the advancement of study, second blood sampling of two rats from three groups was done on 8th day. After the confirmation, no treatment was given to group 2 (disease control) rats. Rats in group 3 received Silymarin 100 mg/kg[16] through intragastric gavage once daily and group 4 was treated with Coffee once daily in the morning. Preparation of coffee involved mixing of coffee powder in boiling water and then filtering it on paper. 200mg/kg[17] dose was given to the rats through gavage method. On day 21 after giving anesthesia with chloroform, blood samples from all the rats which were not in the fasting state, were drawn through cardiac puncture by 3 cc syringe. After clot formation, blood samples were centrifuged at 3500 RPM for 5 min[18] by Bench top centrifuge. In tubes serum was separated for final biochemical estimation which was done on same day by using ALT kit (Merck) and AST kit (Merck) on Chemistry analyzer. Mean± SEM of all four groups was calculated and for comparison post-hoc Tukey test was done. All this was analyzed statistically by using SPSS 20. P value less than 0.05 was chosen significant for the results obtained.

Results

Transaminase levels were increased significantly ($p<0.05$) in rats of group 2 (disease control) due to treatment with Acetaminophen as compared to group A (normal control). Results obtained in group 4 (Coffee treated) showed significant reduction in serum biomarkers as compared to group 3 rats who were treated with Silymarin. Summary of results is as followed:

Discussion

Raised levels of transaminases i.e. ALT and AST makes them important for diagnosis, confirmation as

Table I: Mean ± SEM of ALT and AST Values among All Groups

Groups n = 10	"ALT"	"AST"
Group 1	36.40 ± 3.655	40.20 ± 3.397
Group 2	157.60 ± 7.827	129.00 ± 8.637
Group 3	91.00 ± 1.517	75.80 ± 2.709
Group 4	69.60 ± 3.600	65.40 ± 2.337
p value	<0.05*	

*= Sig value

ALT = Alanine aminotransferase,

AST= Aspartate aminotransferase

Table II: Post -Hoc -Comparison of "ALT" and "AST" B/W Groups

Comparison Of Groups	ALT "Mean difference"	AST "Mean difference"
Group 1 vs. group 2	-121.200*	-88.800*
Group 1 vs. group 3	-54.600*	35.600*
Group 1 vs. group 4	-33.200*	-25.200*
Group 2 vs. group 3	66.600*	53.200*
Group 2 vs. group 4	88.000*	63.600*
Group 3 vs. group 4	21.400*	10.400*

*= Significant

ALT= Alanine –Amino -transferase,

AST= Aspartate –amino –transferase

well as for determining the extent of liver damage clinically and experimentally. The present study showed reduction in transaminase levels of group 3 and group 4 rats which were given silymarin and coffee. But coffee ameliorated the hepatic damage more significantly as compared to silymarin.

In this study, single intraperitoneal injection of Acetaminophen 300mg/kg is used to induce acute liver injury in rats of experimental groups (group 2 to group 4) which resulted in significant increase in serum ALT and AST levels as compared to normal control group 1. And then group 2 is taken as disease control group. This study is supported by the study done by Jersiah and colleagues who used 300 mg/kg dose of Acetaminophen intraperitoneal injection in rats to cause the acute hepatotoxicity and increased "ALT" and "AST" levels in rats.[19]

Silymarin[9] and Coffee[20], both are derived from plants and each one has hepatoprotective activity owing to their antioxidant potential. Special attention has been given to Coffee in the present study as it is also commonly consumed beverage by the people.[10] Comparison has been done with Silymarin, a standard drug that is not something new for liver patients but its bad taste and low bioavailability are the limitations of its usage. According to results, reversal of hepatic damage in the rats was seen with the usage of Silymarin 100mg/kg in group 3. The reversal is due to its membrane stabilizing activity which prevents leakage of intracellular enzymes. This is supported by the study of Godswill J.Udom who investigated the hepatoprotective properties of ethanol seed extract of *Citrus paradisi Macfad* (Grape Fruit) against paracetamol-induced hepatotoxicity in wistar rats.[21] Our results of ALT and AST of group 3 are also in concordance with the study of Bektur and colleagues who studied the Protective effects of Silymarin against acetaminophen-induced hepatotoxicity and nephrotoxicity in mice.[8]

Significant difference in the means of biochemical parameters of group 4 (Coffee 200mg/kg) as compared to the means of group 2 showed that Coffee improved the signs of liver damage and showed reversal of inflammatory signs. Hepatoprotective activity is due to the phenolic content in the coffee that prevents lipid peroxidation against free radicals. Moreover Caffeine and NA block TGF-b and enhance apoptosis of hepatic stellate cells.[22] These results are in accordance with Ibrahim Halil Bahcecioglu who studied serum marker levels and histopathology in *Pistacia terebinthus* Coffee protects against thioacetamide-induced liver injury in rats which showed the preventive effect against experimental hepatotoxicity.[23] Jonathan Arauz studied Coffee consumption prevents fibrosis in a rat model that mimics secondary biliary cirrhosis in humans and concluded that increase in liver function tests was completely mitigated by Coffee in accordance with results of this research.[24] Federico Salomone studied that Coffee enhances the expression of chaperones and antioxidant proteins in rats with non-alcoholic fatty liver disease and concluded that there was a reduction in serum markers in the rats fed on high fat diet plus coffee to healthy control levels.[25]

There was also a significant difference of results between group 3 and group 4 which showed that both agents used for the reversal of APAP induced hepatotoxicity showed improvement in the biochemical parameters but Coffee was better than Silymarin in improving the LFTs.

Conclusion

Silymarin and Coffee individually ameliorate the hepatotoxic effects but Coffee has more beneficial hepatoprotective effects than Silymarin in Acetaminophen induced hepatotoxicity in rats. For future, histopathology aspect can be explored .Further, individual constituents of Coffee can be explored for hepatoprotection.

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ORIGINAL ARTICLE

Developmental Status in Children with Severe Acute Malnutrition

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ABSTRACT

Objective: To access the developmental status in children with severe acute malnutrition (SAM).

Study Design: Hospital based observational cross sectional study.

Place and Duration of Study: Department of Pediatrics, The children's hospital and the institute of child health Multan from 1st January 2019 to 15 July 2019.

Material and Methods: A total of 72 patients aged 6-36 months, diagnosed as severely acute malnourished according to World Health Organization criteria, were included in study. Permission was taken from the IRB ethical committee of the hospital. Prior to study a Performa was designed by trained staff and after the permission of parents complete data were collected from patients. All the children were assessed by using Portage Early Education Plan by a trained and expert clinical nurse to evaluate for the specific areas of development affected by malnutrition. Portage Early Education Plan has five development key areas applied up to 5 years. These are self-help, motor skills, cognition, social skills and language. Complete data was analyzed by using SPSS version.21.0. Mean comparison test was applied and Chi square test was applied and *P* value less than 0.05 were considered as statistically significant (MUAC).

Results: Out of 72 patients, 38(52.78%) were male and 34(47.22%) were female. Male to female ratio was 1.11:1. Mean comparison of mid upper arm circumference (MUAC) was correlated with developmental quotient (DQ). Mid upper arm circumference was found to be significant correlation with Motor developmental quotient (DQ) (*p*-value 0.005), cognition developmental quotient (DQ) (*p*-value 0.048) and mean developmental quotient (DQ) (*p*-value 0.03). It was found that significant association with low Motor developmental quotient (DQ) (Chi^2= 4.2, *P*-value= 0.032), low Cognition developmental quotient (DQ) (Chi^2= 3.0, *P*-value= 0.042) and low Mean developmental quotient (DQ) (Chi^2= 3.1, *P*-value= 0.038).

Conclusion: Children with severe acute malnutrition have extreme developmental delay in all five domains i.e. Self-help, motor skills, cognition, social skills and language. This highlights the importance of developmental therapy with management of malnutrition as recommended by WHO manifest of severe acute malnutrition after development therapy. To improve potential outcome of children with severe acute malnutrition, developmental assessment and therapy should be part of severe acute malnutrition program to timely identify and manage neuro disabilities in severe acute malnutrition.

Key Words: *Mean Score Developmental Quotient DQ, Mental Developmental Quotient DQ, Motor Developmental Quotient DQ, Neuro-Developmental Delay, Portage Early Education Program, Severe Acute Malnutrition.*

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Introduction

The first 1000 days of life (conception to 2 years of age) are particularly crucial for both nutrition and child development. Deficiency of macronutrients as well as micronutrients during this phase has direct long term impact on child development and identifies as major risk factor for developmental delay and deficit in cognitive, motor, social skills and impact on school performance and psychomotor development.[1] According to National nutritional survey (NNS) 2018, 17.7% children in Pakistan are wasted, 40.2% children are stunted and 28.9 % under 5 children are undernourished [2.]

A large number of data suggest that stunting at a young age leads to deficit in cognitive impairment and impaired neuromata development.[3, 4] According to Lancet it is now estimated that 66% children in sub-Saharan-African at risk for not reaching their development potential.[5] A large research gap exists in under developed countries where there is a high prevalence of SAM but no data is available regarding the severity of development and behavioral disorders in children treated at nutrition rehabilitation centers. Also there might be a significant or no significant difference in developmental attainment between children with kwashiorkor and marasmus.[6] SAM children may need comprehensively interventions to enhance neurodevelopmental skills.[7] appropriate physical assessment or cognitive tools along with nutritional assessment followed by exercise rehabilitation reveals positive results in SAM.[8] The rationale for carrying out this study in Pakistan is that our country is facing a huge burden of severe acute malnutrition in under 5 year's old children. There is not much local data available therefore this study was planned to assess the development status of children with Severe Acute Malnutrition in order to bridge the gap and emphasis the need of developmental therapy for SAM in addition to nutrition therapy.

Material and Methods

A hospital based observational cross sectional study was designed. This study was conducted in Department of Pediatrics, The children's hospital and The Institute of child Health Multan From 1st January 2019 to 15 July 2019. A total number of 72 patients aged 6-36 months who were diagnosed as severely acute malnourished according to WHO criteria were included in current study. Simple random sampling technique was used to include maximum children. Prior to study permission was taken from the ethical committee of the hospital. Severe acute malnutrition is defined by a very low weight for height (below -3z scores of the median WHO growth standards), MUAC 11.5 cm or less, or by the presence of nutritional edema.[2] The Children with primary malnutrition were enrolled for this study and all patients with malnutrition secondary to chronic disease were excluded. The parents who did not give the consent, and/or complete data and children with secondary malnutrition were excluded from current study. Once the children with SAM were admitted at NRC of CH & ICH, Multan. They were assessed for infections and illness i.e. diarrhea, liver dysfunction, electrolyte imbalance and pneumonia and have failed an appetite test (defined as an inability to eat therapeutic food).[9] During the stabilization phase, when all the children were stabilized, the complications were dealt with and therapeutic feeding was started and the children entered rehabilitation phase child's developmental was assessed. Prior to study, a Performa was designed by medical officer and after the permission of parents complete data were collected from patients. All relevant data were recorded on performa by the trained nursing staff of hospital. In CH&ICH Developmental pediatrics OPD Portage is applied by psychologist to patients with delayed development, mental age assessed and sessions are started to overcome deficits by psychiatrists. Portage Early Education Plan is internationally applied early childhood interventions service for pre-school children for special needs. A trained and expert clinical psychiatrist with more than 5 years of experience working with Portage Early Education Plan, administered and assessed the child in a quiet room with peaceful surroundings in the Nutrition Rehabilitation Centre. During the assessment mother/care giver of the child was constantly present to comfort the child. Portage Early Education Plan has five development key areas applied up to 6 years. These are self-help, motor skills, cognition, social skills and language. Each area had a specific checklist according to age. Total numbers of checklist items up to 3 years are motor: 63, Cognition: 40, Self-help: 52, Socialization: 43 and Gross motor: 144.In addition, there is a section of infant stimulation activities, which has total 45 checklist item. Child was assessed according to checklist items. When there were 10 consecutive negative items, the nurse at that point of checklist stops. Positive items were obtained by subtracting failure items from total. Developmental age was assessed by first subtracting failures from total to calculate positive items (Total – failure = positive items). Than the positive items were divided by total items and then multiplied by 12 to find out developmental age (Development age=positive item/total item × 12). Developmental age is used to access his/her developmental quotient

respectively by: DQ=DA/Chronological age × 100).

All the children were further assessed in all the clusters of both domains to evaluate for the specific areas of development affected by malnutrition. Data collected was nonparametric. Complete data was analyzed by using SPSS version.21.0. Mean comparison test was applied and chi square test was applied and *P* value less than 0.05 were considered as statistically significant.

Operational Definitions

Severe Acute Malnutrition

Severe acute malnutrition is defined by a very low weight for height (below -3z scores of the median WHO growth standards), by visible severe wasting, MUAC<11.5, or by the presence of bilateral edema[1]

Results

Out of 72 male to female ratio was 1.11:1. Mostly patients 48(66.67%) belong to rural areas and 52(72.22%) patients belong to very low socio-economic status and 44(61.11%) mothers were illiterate. Mean age was 18.23 months and mean weight was 6.74kg. (Table-I).

Table I: Socio-Demographic Characteristics in Children with Developmental Delay

Characteristics	Frequency	Percentage
Gender		
Male	38	52.78 %
Female	34	42.22%
Type of family		
Joint	50	69.44%
Nuclear	22	30.56%
Socio-economic status		
Normal	16	22.22%
Poor	52	72.22%
Good	4	5.56%
Area		
Urban	24	33.33%
Rural	48	66.67%
Mothers Education		
Primary	22	30.56%
Middle	0	0
Matric	6	8.33%
Illiterate	44	61.11%

Table II: Weight for Age Distribution in Children with SAM

Weight for age	Frequency	Percentage
<-3SD	35	48.61%
< -4 SD	37	51.39%

Mean comparison of MUAC was correlated with developmental quotient (DQ). MUAC was found to be significant correlation with Motor QD (*p*-value 0.005), cognition DQ (*p*-value 0.048) and mean DQ (*p*-value 0.03) (Table III).

Table III: Mean Comparison of MUAC and Motor, Mental and Mean DQ

MUAC		DQ- Gross motor	DQ-Cognition	DQ-Mean score
<11.5	Mean±SD	73.5±22.6	75.7±21.4	74.6±22.5n
	P-value	0.005	0.048	0.003

Significant association was found between moderately stunted patients and low Motor DQ (Chi^2= 4.2, *P*-vlaue= 0.032), low Cognition DQ (Chi^2= 3.0, *P*-vlaue= 0.042) and low Mean DQ (Chi^2= 3.1,*P*-vlaue= 0.038) (Table: IV).

Table IV: Height for Age and Motor, Cognition and Mean DQ

Height for Age	Total patients	DQ Motor-Normal	DQ Motor-low	DQ Cognition normal	DQ Cognition low	DQ-Mean normal	DQ-Mean low
<-2SD	35	12	18	12	17	12	18
<-3SD	37	5	37	9	34	7	35
Total	72	17	55	21	51	19	53
		Chi^2= 4.2, *P*-vlaue= 0.032		Chi^2= 3.0, *P*-vlaue= 0.042		Chi^2= 3.1,*P*-vlaue= 0.038	

Discussion

Portage Early Education Program (PEEP) began in Great Britain and is now practiced worldwide for developmentally delayed children. The portage checklist is an ideal instrument for carrying out assessment and setting teaching objectives. It has five main sections each one having total number of items (motor: 140, Cognition: 108, Self-help: 108, Socialization: 83 and language: 218).[8]

The current hospital based observational cross sectional study included children with severe acute malnutrition. These children were assessed using Portage Early Education Program (PEEP) and all of them had low mental and motor DQ. Furthermore, our results show a significant difference in motor and mental DQ of SAM children with stunting and non-stunting. The socio-economic status was also found to be significantly related with under nutrition. Our study is distinctive as it uses PEEP to assess developmental status of children with SAM.

First three years of life are generally counted as a very crucial for children's development. Most recent studies focus on effects of undernutrition in young

children's development aged less than 36 months. Our study also included under 5 years children with severe acute malnutrition and Majority of children with 3SD SAM also had low Motor DQ, low cognition DQ and low mean DQ. Another study by Dwivedi D et.al, also observed similar low motor and mental DQ in Indian children with SAM. These studies show that severe acute malnutrition at early stages of child development is strongly linked with child performance on school level and it negatively effects fine motor skills, personal-social, language, gross motor skills and social-emotional competences of SAM children as compared to non-SAM.[10,11] There was a significant difference in motor and mental DQ of SAM children with stunting and non-stunting in our study. The comparison of stunted and non-stunted children with developmental quotient was analyzed between two groups which shows that patient with stunting has low development assessment scores as compared to non-stunted children. Similarly conducted studies were also show same results.[12] However there were low emphasis on behavioral alterations and outcomes of children with SAM and stunting e.g. higher negative impact, lesser physical activity, play and exploration and interactions with other children.[13]

In the present study mostly male children 52.78% were affected by severe acute malnutrition similar results were also found in another research showing higher male to female ration of SAM children, the reasons for this higher male to female ratio is still unknown as more importance is given to male child in our culture and they are better taken care of[14,15] Children with SAM show significant delay in development, but motor DQ is affected more than mental DQ, these findings were reinforced by different studies conducted in India on similar topics.[11,16] The comparison of MUAC and Development Quotient was done and it was reported that Motor DQ, Mental DQ and Mean DQ was significantly low in children having MUAC 11.5cm. Higher MUAC and anthropometric z -scores, including height-for-age, were related to higher development. The findings show a direct relation of MUAC and Motor DQ, Mental DQ and Mean DQ but another study show that mental DQ was insignificant and unrelated to MUAC, indicating MUAC as irrelevant to mental DQ.[17,18] The socio-economic status is significantly related with under nutrition in our study as 72.22% children's had very low socio-economic status and it slightly higher as compared to study conducted by Ullah et al.[19]

The overall low level of development in children with SAM in this study is distressing. This study was conducted on a small sample size with limited resources. To produce more significant results more studies should also be conducted using Portage Early Education Program (PEEP) in different provinces of Pakistan to assess which dimensions of child development is impaired during the acute stage of SAM in children under 5 years of age. Similar studies with different development assessment tools e.g Bayley Scales of Infant Development should be conducted to figure out the most suitable tool for our native culture.

Conclusion

Children with Severe acute malnutrition have extreme developmental delay in all five domains i.e. self-help, motor skills, cognition, social skills and language. This highlights the importance of developmental therapy with management of malnutrition as recommended by WHO manifest of severe acute malnutrition after development therapy. To improve potential outcome of children with severe acute malnutrition, developmental assessment and therapy should be part of severe acute malnutrition program to timely identify and manage neuro disabilities in severe acute malnutrition.

Limitations of the Study

The limitations of this study includes small sample size and limited time duration. The developmental assessment was done in the rehabilitation stage only, there was no information about the developmental status of child before or after admission. Children should be followed up after nutritional rehabilitation and developmental therapy to assess outcome. Culturally adapted assessment tools for development be designed and used for assessment as the international portals are not suitable for our local children.

Funding's and Conflict of Interest

The research was funded by the authors and no external grant was taken or used for the purpose of this research. There is no conflict of interest in this study as well.

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ORIGINAL ARTICLE

The Ameliorative Effect of Ginger on Cadmium Induced Histological Changes in Testes of Albino Rats

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ABSTRACT

Objective: To study the ameliorative effect of ginger against histological changes induced by cadmium in testes of albino rats.

Study Design: Randomized control trial.

Place and Duration of Study: The research was conducted at animal house, National Institute of Health (NIH), Islamabad. The research was carried out for one year of duration from 1st November 2017 to 28 November 2018.

Material and Methods: Forty-five male adult albino rats were included via simple random sampling technique. Using balloting method, each subject was randomly allocated into one of the three groups. Distilled water was orally given to rats of control group I. The rats of group II were provided with cadmium chloride while group III received cadmium as well as ginger in selected doses orally for 28 days. Dissection was done after 28 days and testes were observed for histological changes.

Results: The use of ginger ameliorates the gross and microscopic changes induced by cadmium in testes of Albino rats of group III as compared to group II rats, which received only cadmium**.** Among microscopic qualitative parameters, infiltration, congestion and necrosis were markedly reduced by use of ginger in group III rats.

Conclusion: The use of ginger improves the histological changes induced by cadmium in testes of albino rats.

Key Words: *Cadmium Chloride, Ginger, Rats, Testis.*

Introduction

Testis is an important sexual organ which enables spermatogenesis and secretion of male sex hormones. This function is highly necessary for continuity of life. Among mammals, when considering a rat, the structure of rat testis is comparable to humans and has been a source of comparative study. Its testis measures 1x2x1.5cm.[1] Environmental toxins affect the function of testis; cadmium is one of them. It acts as catalyst in the production of reactive oxygen species; decreasing protein bound sulfhydryl groups and glutathione, thus increasing lipid peroxidation and oxidative stress.[2] However, the tissue damage caused by cadmium may be ameliorated by the use of certain herbal agents acting as antioxidants like ascorbic acid, zinc, garlic, turmeric, cinnamon and ginger.[3] Ginger has beneficial effects on cardiovascular system, reproductive system and gastrointestinal system.[4] The concentration of volatile oils present in ginger is 1% to 3%. The main constituents are sesquiterpenes, beta-bisabolene and zingiberene. Zingiberol and zingiberenol are other; all play an active role as anti-oxidants, anti-microbials and anti-inflammatory when introduced in mammals. Hence, ginger has been used in multiple clinical trials to check its efficacy as a protective agent against harmful substances.[5]

Cadmium is one of the important components used in rechargeable nickel- cadmium batteries, aircraft industry and television picture tubes. Hence, there's a certain degree of probable exposure to the personnel working in one of these industries.[6] Besides acute and chronic kidney damage, cadmium causes carcinoma of lung, kidney and prostate. Cadmium has acute and chronic effects on various organs of body including lungs, kidney, prostate and

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bones.[7] Ginger has been proved to be an effective antioxidant for cadmium induced damage on organs such as liver[8] and kidenys.[9] However, there is minimal evidence in literature, specifically the local research base, which proves the advantages of ginger against cadmium in the reproductive system. Hence, the aim of this study was to assess the protective role of ginger against cadmium induced toxicity in testicular cells on a gross and microscopic level.

Material and Methods

The study was carried under supervision of animal house at National Institute of Health (NIH), Islamabad. The study was conducted from 1st November 2017 to 28th November 2018. A total of 45 male rats were procured by employing simple random sampling technique with balloting method[10] and were kept in a controlled standard living environment at the animal house of NIH. The study design was Randomized Controlled Trial. Prior to the initiation of the study, the research was approved by Ethical Review Committee (ERC) of Islamic International Medical College (IIMC).

Eight weeks old healthy male albino rats of Sprague Dawley strain weighing 140-220 gm were selected for the study, while those with any congenital or pathological abnormalities were excluded.

The rats were randomly allocated into 3 groups of 15 rats each and were kept in cages, in a controlled standard living environment in a well-ventilated room with cycles of 12 hour day and night, and temperature maintained between 20 to 26 °C. Group I (control) rats received distilled water as drinking water for 28 days. Group II rats received orally a solution of cadmium (03mg/kg/day) as cadmium chloride for 28 days. Group III rats consumed orally a solution of cadmium (03mg/kg/day) as cadmium chloride along with ginger 500mg/kg/day for 28 days. All rats were euthanized and dissected after 28 days. Testes were explored and taken out of scrotum. The tissues were fixed, embedded in paraffin blocks and stained with eosin and haematoxyline. The slides were examined in detail under 10X and 40X power of light microscope. Gross features including color, appearance, texture and weight were noted. Microscopic examination was performed to observe parameters including the presence of congestion of blood vessels in stroma, infiltration of inflammatory cells in stroma and change in epithelial height in seminiferous tubules in micrometers.

Data was entered and analyzed using Statistical Package for Social Sciences (SPSS) version 22. Mean and standard error were calculated for the quantitative variables. Categorical variables were represented by frequency and percentage. Chi square test was applied for comparison of qualitative variables. Data was tested for normality with Kolmogorov-Smirnov and Shapiro-Wilk tests. One way analysis of variance (ANOVA) was applied for the mean comparison of quantitative variables between control group I and experimental groups II and III.Post hoc Tukey's test was applied for multiple comparisons of these three groups. The results were analyzed and considered significant with P value less than 0.05.

Results

The color of testes ranged from pink, yellow and light pink in group I, II and III respectively. Group I showed normal appearance while group II and group III showed shrunken and swollen appearances respectively. The texture of the testes was soft in case of group I while group II and group III were having hard textures. (Table I) Regarding weight of the testes, in group II (Mean=1.96, SEM=0.074) it was reduced compared to group I (Mean=2.43, SEM=0.105) and again increased in group III (Mean=2.30, SEM=0.087) which received ginger ($p<0.001$). Table II shows the group wise multiple comparisons.

All blood vessels were normal and congestion (Figure 1a) was absent in all rats of group I while testes of rats of group II were congested. In group III, 47% of rats showed congestion of blood vessels while 53% showed normal blood vessels. There was significant

Table I: Color, Appearance and Texture of the Three Groups

	Group I	Group II	Group III	P-value
Colour	Pink (100%)	Yellow (100%)	Light Pink (100%)	<0.001
Appearance	Normal (100%)	Shruken (73.3%) Normal (26.7%)	Swollen (60%) Normal (40%)	<0.001
Texture	Soft (100%)	Hard (73.3%) Soft (26.7%)	Hard (46.7%) Soft (53.3%)	<0.001

Table II: Multiple Comparison of Weight (G) of Testis among Control and Experimental Groups of Albino Rats

Groups	Mean Difference	*p* value
I vs II	3.26	0.002
I vs III	1.24	0.349
II vs III	2.03	0.068

difference ($p<0.001$) between presence of congestion of blood vessels in all groups (Table III). Inflammatory cells were absent in all testes of rats of group I while present among all rats of group II. In group III, 53% of testes showed infiltration of inflammatory cells while 47% rat's testes showed no infiltration. Results were significant in all groups. ($p<0.001$) (Figure 1).All the testes of group I showed mean epithelial height (58.500µm) of seminiferous tubules. In group II the mean epithelial height of seminiferous tubules was 44.833 µm. In group III the mean epithelial height of seminiferous tubule was 54.000µm. significant difference was found in mean epithelial height in all groups.($p<0.0001$) (Table IV) while multiple groups comparison showed significant difference among all groups.

Table III: Group Wise Distribution of Congestion of Blood Vessels and Focal Necrosis among Control and Experimental Groups of Albino Rats

	Presence of Congestion of Blood Vessels n=15			Prensence of Inflamatory Cells in the Stroma n=15		
Groups	Present (%)	Absent (%)	*P*value	Present (%)	Absent (%)	*p* value
Group I	0 (0 %)	15 (100 %)	<0.001*	0 (0 %)	15 (100 %)	<0.001*
Group II	15 (100 %)	0 (0 %)		15 (100 %)	0 (0 %)	
Group III	7 (46.7%)	8 (53.3%)		7 (46.7%)	8 (53.3%)	

Table IV: Group Wise Distribution of Height of Seminiferous Epithelium among Control and Experimental Groups of Albino Rat's *p* ≤0.001

	Height of Seminiferous Epithelium in µm n=15				
Groups	Mean	SEM	Multiple comparisons		
I	58.50	1.39	I vs II	13.66	<0.001
II	44.83	1.30	I vs III	4.50	0.053
III	54.00	1.26	II vs III	9.16	<0.001
p value	<0.001				

Discussion

Exposure to cadmium is inevitable[11] and the subsequent deleterious effects on the testes are highly likely. Being an important organ for spermatogenesis, the testes also play an important role in production of male sexual hormones and male growth and development.[12] However, heavy metals such as arsenic, cadmium and nickel bring molecular changes in the structure of testicular cells which lead to decline in the functional ability of the organ.[13] However, as proven with the current study these effects can be reduced, if not prevented, by maintaining levels of herbs such as ginger. Hence, testicular viability, potency and function can be preserved. Other materials used in various studies have been proven to be potent in delaying testicular toxicity such as quercetin, grape seed extracts, zinc and magnesium.[14,16] Ginger, on the other hand, has been proved to have protective role by antagonizing reactive oxygen species.[17]

Congestion of vessels was seen as an effect of cadmium in our study, it was 100% in group II, but with the use of ginger it reduced down to 46.7%. In the study conducted by de Souza, cadmium was given to three different groups at different doses of 0.1 and 1.2mg per kg for 8 weeks, they showed congestion in blood vessels.[18]Manca D also conducted a study in which cadmium chloride was given in doses of 1mg and 10mg for 45 and 90 days respectively and testis showed congestion in blood vessels.[19]In a study by El-Sharkawya, when ginger extract was given, then congestion in blood vessels was remarkably decreased in testes of rats.[20]

The works of Schlaepfer[21] and Mouro[22]showed that seminiferous epithelium damage by cadmium results from hypoxia due to alteration in intratesticular blood flow. This effect leads to accumulation of inflammatory cells within the testis.[23]These findings were further validated with the current study in which group II had the highest degree of inflammatory cells, but since group III had reduced inflammatory cells, it proves the protective role of ginger in reducing the cadmium induced inflammatory response.

The study can be further extended by investigating the dose dependent effects of Cadmium. Moreover, the effects of route of administration and duration of use can be studied as well. As immunological effects

of Cadmium have been suggested at cellular level, so cyto-immunological analysis may be included.[23] Furthermore, the changes at the level of genetic expression may be considered. This would give a deeper view on the mechanisms behind the protective effects of ginger and may be extended towards other chronic autoimmune and inflammatory diseases.

Conclusion

Cadmium exposure causes gross and histological changes in the testes of albino rats. The use of ginger significantly reduces the development of the changes; effectively providing complete protection to at least half of the exposed population. Further larger scale and long-term trials are recommended to have an insight on exact mechanisms.

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ORIGINAL ARTICLE

Barriers in Handoffs among Nurses in Public Sector Tertiary Care Hospital of Peshawar, Pakistan

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ABSTRACT

Objective: To identify barriers in shift handover communication among nurses in public sector tertiary care hospital of Peshawar, Pakistan.

Study Design: Cross-sectional study.

Place and Duration of Study: The study was conducted in Hayat Abad Medical Complex Peshawar, Pakistan from November, 2016 to August 2018.

Material and Methods: Sample size was comprised of 112 registered nurses, selected by simple random sampling technique. All the included registered nurses had minimum one year of experience. Those working at the managerial level, who did not participate in handovers, were excluded. Adopted questionnaire of closed-ended questions was used for data collection. Mean and standard deviation were calculated for age. Descriptive statistics of percentages and frequencies were utilized for responses of participants and demographic characteristics of gender, education and experiences. Chi square test was employed to analyze association of gender and barriers (p-value<0.05).

Results: Alarming barriers revealed were messy records (91.1 %), unreadable handwriting (83.1%), out-of-date records (76.8%), poor communication skills(80.4%), not listening and interruption (73.2%), irrelevant information (77.7%), handover with junior/senior (70.6%) and disagreement between clinicians(70.5%), unavailability of relevant information (83.4%), unavailability of doctors (81.3%), background noise (75.9%), staff shortage (75.9%) and poor workforce planning (79.5%). No significant association was found between gender and barriers to shift handover (p-value >0.05) except for unavailability of test results at the time of handover (p-value = 0.02) and difficulty to recognize essential information (p-value = 0.007).

Conclusion: The study identified various barriers in public sector hospital which may negatively affect shift handover.

Key Words: *Barriers, Communication, Registered Nurse, Shift Handover.*

Introduction

Clinical handovers are considerably precarious activities that require substantial coordination and outstanding communication to sustain continuity in patients' care.[1,2] The process of handover serves multiple functions but the most essential one is the transfer of authority, accountability and responsibility of patients' care from the departing health care provider to the upcoming health care provider.[3,4,5] Change of shift require nurses to share vital information that will guide the team of next shift in the continuity of patients' care but this is generally impeded.[6]

Despite positive functions, the process of shift handovers is likely to be problematic, plentiful of risks and hazards, inevitably resulting in active and passive failure.[7] Ineffective handovers contribute to medical error, delayed and inappropriate treatment, adverse event of minor and major harms, extended hospitalization, preventable readmissions and expanding cost of treatments.[4] Similarly evidences revealed that ineffective shift handover increases the chances of medication errors and decreases patients' satisfaction.[8] Researches estimate that patients are 40% more likely to die in ICU than the traffic accidents.[9]

There are multiple reasons for ineffective handovers

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reported by previous literature. It has been demonstrated that handovers are often informal and are faced by potential threats including noise, crowding, heavy workload, interruptions and patients' care activities.[10]

In our country, Pakistan, shift handovers in public sector hospitals are largely communicated verbally and without utilizing any integrated protocol. In absence of an integrated protocol and appropriate environment, patients' care information is not properly communicated. Subsequently, this leads to increased risk of medical errors, loss of continuity in care and adverse events to patients' safety[11] unfortunately, no previous study was found in the context of Pakistan regarding shift handover. Thus there is a dire need to conduct a study and explore the related issues to the subject. The study was conducted to identify barriers in shift handover communication among nurses in public sector tertiary care hospital of Peshawar Pakistan.

Material and Methods

The study was conducted from November, 2016 to August, 2018 at public sector tertiary care hospital Hayatabad Medical complex (HMC) of Peshawar, Pakistan by utilizing the cross-sectional research design. Total 112 registered nurses were selected through simple random sampling technique. Slovin's formula ($n = N/1+N(e)^2$ was used to calculate the sample size. The inclusion criterion was to include all the nurses of Hayatabad Medical Complex not less than one year of experience. All those nurses who did not participate in the shift handover were excluded from the study. These registered nurses were mostly at managerial level.

An adopted questionnaire was utilized for data collection with a few modifications.[12] The questionnaire was related to barriers in shift handover communication, containing two parts. The first section was related to demographic characteristics while the second section revealed the potential barriers to shift handover communication. The questions were in the form of Likert scale having options of strongly agree, agree, disagree and strongly disagree. There were 38 categorical variables in the questionnaire. The responses of the participants were considered alarming when the responses shown agreement of ≥70%. For the same reason the Likert scale responses were converted into dichotomy, strongly agree/agree into agree and disagree/strongly disagree into disagree to minimize the differences in extreme responses and for simplification of analysis.

The approval of study was obtained from the Ethical Committee of Khyber Medical University (KMU) Peshawar. The purpose of the study was explained to participants before filling in of the consent form and the questionnaire.

Data were entered and analyzed by utilizing SPSS 22. Mean and standard deviation were calculated for age of the participants. Descriptive statistics of frequencies and percentages were used for responses of participants and demographic characteristics of gender, level of education and the duration of experiences. Chi-square test was employed to analyze the relationship between gender and barriers to shift handover communication. The p-value of 0.05 was considered significant (CI 95%).

Results

A total of 112 nurses completed and returned the questionnaires. Of the participants 16(14.3%) were male and 96 (85.7%) were female. Approximate mean age of the participants was 27.86(SD= 4.57). Majority of the registered nurses 77(68.8%) had diploma in general nursing, 33(29.5%) were post RN and 2 (1.8%) were generic BScN.

Individual Barriers to Shift Handover among Nurses

The alarming barriers found were: messy records (91.1%), unreadable handwriting (83.1%), out-of-date records (76.8%), poor communication skills (80.4%), not listening and interruptions (73.2%), irrelevant information (77.7%), handover with more junior and senior staff (70.6%), and disagreements between clinicians regarding patients' condition (70.5%). Only incorrectly record information (66.9%) were not alarming barriers. (Table-I)

Environmental Barriers to Shift Handover among Nurses

The alarming barriers were: unavailability of the relevant information (83.4%), the doctor of previous shift is not available for responses (81.3%), background noise (75.9%) and poor workforce planning (79.5%). (Table-II)

Association between Individual Barriers and Gender (Male and Female)

All barriers existed equally among gender (male &

Table I: Individual Barriers to Shift Handover Communication

Individual Barriers	Strongly Agree	Agree	Disagree	Strongly disagree	Dichotomy	
					Agree	Disagree
Messy records	58 51.8%	44 39.3%	7 6.3%	3 2.7%	102 91.1%	10 8.9%
Unreadable handwriting.	17 15.2%	76 67.9%	16 14.3%	3 2.7%	93 83.1%	19 17%
Out of date records.	25 22.3%	61 54.5%	22 19.6%	4 3.6%	86 76.8%	26 23.3%
Poor communication skills.	31 27.7%	59 52.7%	19 17.0%	3 2.7%	90 80.4%	22 19.9%
Not listening and interrupting.	37 33.0%	45 40.2%	25 22.3%	5 4.5%	82 73.2%	30 26.8%
Irrelevant information during handover.	28 25.0%	59 52.7%	21 18.8%	4 3.6%	87 77.7%	25 22.4%
Difficulty to recognize essential information	23 20.5%	52 46.4%	33 29.5%	4 3.6%	75 66.9%	37 33.1%
Handover communication with more junior/senior members of staff.	31 27.7%	48 42.9%	28 25.0%	5 4.5%	79 70.6%	33 29.5%
Disagreements between clinicians regarding a patient's condition.	23 20.5%	56 50.0%	27 24.1%	6 5.4%	79 70.5%	33 29.5%
Incorrectly recalled information.	18 16.1%	50 44.6%	36 32.1%	8 7.1%	68 60.7%	44 39.2%

Table II: Environmental Barriers to Shift Handover Communication

Environmental Barriers	Strongly Agree	Agree	Disagree	Strongly disagree	Dichotomy	
					Agree	Disagree
Unavailability of relevant information	26 23.2%	67 59.8%	11 9.8%	8 7.1%	93 83.4%	19 17%
The doctors of previous shift is not available for responses to queries	21 18.8%	70 62.5%	20 17.9%	1 0.9%	91 81.3%	21 18.8%
Unavailability of relevant tests results	23 20.5%	48 42.9%	39 34.8%	2 1.8%	71 63.4%	41 36.4%
Interruptions by patients relatives	24 21.4%	54 48.2%	30 26.8%	4 3.6%	78 69.6%	34 30.4%
Interruptions by colleagues.	19 17.0%	47 42.0%	44 39.3%	2 1.8%	66 58.9%	46 41.1%
High background noise levels.	23 20.5%	62 55.4%	23 20.5%	4 3.6%	85 75.9%	27 24.1%
Long working hours.	23 20.5%	54 48.2%	28 25.0%	7 6.3%	77 68.8%	35 31.3%
Staff shortages.	23 20.5%	62 55.4%	23 20.5%	4 3.6%	85 75.9%	27 24.1%
Short time for shift over.	17 15.2%	53 47.3%	38 33.9%	4 3.6%	70 62.5%	42 37.5%
Poor workforce planning (for example, poor organization of staff)	26 23.2%	63 56.3%	23 20.5%	0 0.0%	89 79.5%	23 20.5%
The division of responsibility is unclear.	22 19.6%	54 48.2%	32 28.6%	4 3.6%	76 67.9%	36 32.1%

female). No significant association was found between the individual barriers to shift handover communication and gender (male and female) (p-value >0.05) except for difficulty to recognize essential information (p-value = 0.007). (Table-III)

Table-III: Association Individual Barriers to Gender (Male % Female)

Individual Barriers	Gender	Agree	Disagree	p-value
Messy records	Male	11.6%	2.7%	0.137
	Female	79.5%	6.3%	
Unreadable handwriting	Male	13.4%	0.9%	0.217
	Female	69.6%	16.1%	
Out of date records	Male	9.8%	4.5%	0.411
	Female	67.0%	18.8%	
Poor communication skills	Male	9.8%	4.5%	.207
	Female	70.5%	15.2%	
Not listening and interrupting	Male	9.8%	4.5%	0.663
	Female	63.4%	22.3%	
Irrelevant information during handover	Male	10.7%	3.6%	0.781
	Female	67.0%	18.8%	
Difficulty to recognize essential information	Male	5.4%	8.9%	0.007
	Female	61.6%	24.1%	
Handover communication with more junior/senior members of staff	Male	9.8%	4.5%	0.866
	Female	60.7%	25.0%	
Disagreements between clinicians regarding a patient's condition	Male	12.5%	1.8%	0.108
	Female	58.0%	27.7%	
Incorrectly recalled information	Male	8.0%	6.3%	0.693
	Female	52.7%	33.0%	

Chi square test applied, CI= 95%

Association between Environment Barriers and Gender (Male and Female)

All the barriers to shift handover existed equally among gender. No statistically significant association was shown between the environmental barriers to shift handover communication and gender (male & female) (p-value>0.05) except for the unavailability of the tests' results (p-value = 0.02) which is more prevalent in female than male.

Discussion

The findings of the study revealed messy records as the most common barrier in public sector hospital. Conventionally most of the documentation is manual in public sectors hospitals in our country and there is no appropriate filing of the documents of the relevant papers. No systematic way of filing is followed and papers are usually scattered. Thus it is

Table-IV: Association of Environmental Barriers to Gender (Male & Female)

Environmental Barriers	Gender	Agree	Disagree	p-value
Unavailability of relevant information	Male	10.7%	3.6%	0.355
	Female	72.3%	13.4%	
The doctors of previous shift is not available for responses to queries	Male	11.6%	2.7%	1.000
	Female	69.6%	16.1%	
Unavailability of relevant tests results	Male	5.4%	8.9%	0.020
	Female	58.0%	27.7%	
Interruptions by patients relatives	Male	12.5%	1.8%	0.093
	Female	57.1%	28.6%	
Interruptions by colleagues	Male	6.3%	8.0%	0.183
	Female	52.7%	33.0%	
High background noise levels.	Male	10.7%	3.6%	0.928
	Female	65.2%	20.5%	
Long working hours.	Male	8.9%	5.4%	0.560
	Female	59.8%	25.9%	
Staff shortages.	Male	9.8%	4.5%	0.471
	Female	66.1%	19.6%	
Short time for shift over.	Male	8.0%	6.3%	0.577
	Female	54.5%	31.3%	
Poor workforce planning (for example, poor organization of staff)	Male	11.6%	2.7%	0.849
	Female	67.9%	17.9%	
The division of responsibility is unclear.	Male	7.1%	7.1%	0.099
	Female	60.7%	25.0%	

challenging to provide all the documents at the time of shift handovers. The previous literature has documented messy records as the most central obstacles in shift handovers.[12] Of the participants 83.1% considered that unreadable handwriting was alarming barrier. The same finding has also been mentioned in the previous literature.[13,14] The illegible handwriting may results in due to the heavy work burden or it may be due to the shortage of the staff. The out of dated records were also alarming barriers (76.8%). The finding has also been revealed in a study of Czech Republic.[12] The participants in the current study showed that poor communication skills are responsible for the ineffective communication (80.4%). The result is congruent with findings of the previous studies. [13,15] Similarly the participants concluded that there was lack of approach to proper listening and there were interruptions (73.2%). This barriers has also been discussed in the previous literature.[13,10] In the same way literature has demonstrated that there were 1.25 interruptions per handover.[16]

Usually in handover irrelevant information are provided (77.7%). This finding is in line with the previous literature which reported that too much information is being provided during shift handover including irrelevant informaton.[17]

Sometimes it is difficult to include which types of information in the transition of patients (66.9%). It may be caused by lack of training of nursing staff. This issue has been discussed in the previous literature.[4,13,18] Usually it is difficult for the nursing staff to make proper communication with more senior or junior staff. This problem was identified by 70.6% of the participants. This issue can be conveniently eradicated if appropriate training is provided to the registered nurses. Similarly the disagreement between the physicians may also create a hurdle in the proper communication during shift handover (70.5%). The findings were not mentioned in the previous literatures. Incorrectly recalled information is not an alarming barrier in the study (60.7%). This issue can be better explained by the shortage of staff, unavailability of relevant documents and lack of organized documentation of patients' care. Errors of omission and communication gap have been the factors which negatively affected the handovers despite numerous studies.[19]

The findings revealed that unavailability of relevant information was an alarming barrier and was responded positively by 83.4% participants. Of the participants 80 % responded in one of the qualitative study that little relative information were provided to them during shift handover. This causes them the wastage of time to search for relevant information at the end of the shift.[17] This issue in shift handover may cause delay of treatment and the wastage of time. In one of the Korean study it was reported that relevant information is not being provided in shift handovers with 26% of participants' agreement.[20] Sometimes the unavailability of the doctors may results in the ineffective communication. Of the participants 81.3% showed that doctors were not available for queries in shift handover who were responsible for the patients' treatment in the previous shift. There may be limited organizational monitoring due to which the health care team availability cannot be maintained. Of the participants 63.4% revealed that unavailability of the

relevant test results is hurdle in shift handover. This might be explained in the inconsistent record keeping in the hospital settings.[21]

Of the participants 69.6% were of the opinion that the interruptions of the family member create huddles in the shift handover communication. The finding is in line with other previous studies.[10] The interruptions in shift handover may also be caused by colleagues in the hospitals. In the current study 58.9% of the participants agreed that colleagues interrupt shift handover. The lesser agreement of responses may be due to shortage of staff. If there is low number of staff there might be decreased interruptions by the colleagues. Previous studies have also demonstrated that interruption of colleagues negatively affected the shift handover.[4] High background noise was an alarming barrier responded positively by 75.9% of the participants. This barrier has been mentioned in the previous literature.[16] In our health care facilities the presence of large numbers of family members in the hospital units may be the result of high background noise.

In the current study the long working hours was not shown as alarming barrier (68.8%). This factor has been discussed by a systematic review[13] and a cross-sectional study.[12] Staff shortage negatively affects the shift handover (75.9%). This is one the critical problems of public tertiary care hospitals which has adverse impacts on every aspect of health delivery systems. The previous literature has demonstrated that staff shortage caused delay in handovers and resulted in work burden.[22] Sometimes the division of responsibility is not clear among the staff which results in ineffective shift handover (67.9%). This barrier has also been discussed previously.[13] The unclear responsibility may have been underestimated by the participants due to lack of clear job description and shortage of staff.

The findings in the current study, demonstrated that the handovers of public health care system is confronted with multiple issues. Previous studies have shown that the education and training nursing staff could be beneficial to improve the patients' care and coordination of services. It may include communication skills and the process of handover.[23]

The study has limitation in the context that the participants may not have expressed themselves eloquently because we have used closed-ended questionnaire. In future it is recommended that qualitative studies may be conducted to achieve adequate opinions of the registered nurses. Insufficient representation of the male nursing staff may have caused sampling bias. Comparison of local studies could not be conducted because of the unavailability published of literature. This is the first study to provide an insight into the shift handover in the context of Pakistan. Therefore the study results may be helpful in designing protocol and standardization to improve the current status of shift handover in the country.

Conclusion

The findings show the grim issues that exist in the shift handover. The reflection of these issues is demonstration of the fact that further studies are needed to be undertaken to better understand the background of current status of shift handover. Furthermore the findings call for the incorporation of effective education and training to improve shift handover. This will maximize the safety of the patient and improve the patients' treatment process.

Recommendations

It is recommended in the light of the findings that qualitative and interventional studies may be conducted to better understand the inherited issues in the shift handover in Pakistan. Moreover it is also recommended that an integrated protocol should be employed during shift handover to minimize the negative effects.

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